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Daminozide: Technical Support Document. Special Review Preliminary Determination to Cancel the Food Uses of Daminozide

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This Position Document addresses the risks and benefits of pesticide products containing the subject active ingredient. The Agency has determined that the use of products containing the subject active ingredient may meet or exceed a risk criterion described in 40 CFR Part 154. Potential hazards will be examined further to determine the nature and extent of the risk, and considering the benefits of the subject active ingredient, whether such risks cause unreasonable adverse effects on the environment.

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DAMINOZIDE

SPECIAL REVIEW

TECHNICAL SUPPORT DOCUMENT - PRELIMINARY DETERMINATION TO CANCEL THE FOOD USES OF DAMINOZIDE

MAY, 1989

Office of Pesticide Programs
Office of Pesticides and Toxic Substances
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TABLE OF CONTENTS

Page

Executive Summary.................................... i
Acknowledgements..................................... vi

I. Introduction I-1

A. General Background and Organization........... I-1
B. Legal Background............................ I-1
C. Chemical Background........................... I-2
D. Regulatory History of Daminozide............. I-3
  1. Uses and Registration...................... I-3
  2. Tolerances............................... I-3
D. Analysis of Rebuttal Comments................ I-9

II. Risk Assessment II-1

A. Hazard Identification (Qualitative Risk Assessment)............................ II-1
  1. Oncogenic Effects......................... II-1
  2. Structure-Activity Relationship........... II-9
  3. Mutagenicty............................... II-9
  4. Metabolism................................ II-10
  5. Non-Oncogenic Effects..................... II-12
  6. Human Studies............................. II-13
  7. Weight of the Evidence.................... II-14
  8. Dose-Response Assessment.................. II-19
B. Exposure Assessment.......................... II-21
  1. Dietary Exposure.......................... II-21
  2. Non-Dietary Exposure...................... II-37
C. Risk Characterization........................ II-39
  1. Dietary risks............................. II-39
  2. Non-Dietary Risks......................... II-42
  3. Uncertainties in the Risk Assessment...... II-43

TABLE OF CONTENTS (CONTINUED)

Page

III. Benefits Analysis III-1

A. Introduction.................................. III-1
B. Benefits Assessment - Food Uses.............. III-1
  1. Apples.................................. III-2
  2. Peanuts................................. III-14
  3. Cherries................................ III-16
  4. Grapes.................................. III-18
  5. Peaches and Nectarines.................. III-19
  6. Pears................................... III-20
  7. Tomato Transplants...................... III-21
C. Benefits Assessment - Non-Food Uses
  1. Ornamentals and Greenhouse Plants......... III-22

IV. Development of Regulatory Options IV-1

A. Introduction.................................. IV-1
B. Risk Summary.................................. IV-1
C. Benefits Conclusions.......................... IV-4
D. Regulatory Options IV-6
E. Regulatory Decision........................... IV-10
F. Existing Stocks............................... IV-10

V. Bibliography.................................... V-1

EXECUTIVE SUMMARY

This document contains the Environmental Protection Agency's (EPA's) evaluation of the risks and benefits of the plant growth regulator daminozide and the basis for the Agency's proposed cancellation of the food uses of daminozide.

Daminozide is the accepted, common name for butanedioic acid mono (2,2-dimethylhydrazide). Daminozide (trade name Alar®) was first registered in 1963 by the Uniroyal Chemical Company, Inc., for use on potted chrysanthemums. The first food use of daminozide was registered in 1968 for use on apples. Daminozide is currently registered for use as a plant growth regulator to control vegetative and reproductive growth of orchard crops including apples, cherries, nectarines, peaches, and pears. Daminozide affects flower bud initiation, fruit set and maturity, fruit firmness and coloring, preharvest fruit drop and the market quality of fruit at harvest and during storage. Daminozide is also used to enhance shorter and more erect peanut vines, suppress growth of tomatoes, and modify the stem length and shape of ornamental plants. In 1985, it was estimated that 49-77 percent of the total daminozide usage was on apples, approximately 26 percent of daminozide usage was on peanuts, and 5 percent was on ornamentals. Since 1985, daminozide use on both apples and peanuts has decreased significantly while the non-food uses have remained steady.

On July 18, 1984, EPA issued a Notice of Initiation of a Special Review (which included a Position Document 1 or PD 1) of pesticide products containing daminozide (49 FR 29186). This action was based on the Agency finding that pesticide products containing daminozide met the risk criterion relating to oncogenicity formerly at 40 CFR 162.11(a)(3)(ii)(A) and now found at 40 CFR 154.7(a)(2)(i). At that time, the relevant portion of 40 CFR 162.11 provided that a Special Review shall be conducted if the use of a pesticide "induces oncogenic effects in experimental mammalian species or in man as a result of oral, inhalation or dermal exposure...." Specifically, available data indicated that administration of daminozide and its degradate and metabolite, unsymmetrical dimethylhydrazine (UDMH), to laboratory animals resulted in statistically and biologically significant oncogenic responses at multiple organ sites in multiple species and strains of animals. UDMH was believed to be a very potent animal carcinogen and mutagen.

In September 1985, the Agency developed a Draft Notice of Intent to Cancel and a Draft PD 2/3/4 in which cancellation of the food uses of daminozide on the basis of cancer dietary risk was proposed. The Scientific Advisory Panel (SAP), reviewed the Draft Cancellation Notice and Draft PD 2/3/4 and concluded that the studies relied on by the Agency did not support quantitative cancer risk assessment. The Panel, which was established by Congress to provide scientific review of EPA pesticide actions, believed the data raised concern, but that the studies used by the Agency were sufficiently limited that they were inappropriate for risk assessment.

After consideration of the comments made by the SAP, the Agency decided to postpone any further activity on the cancellation action at that time. However, the Agency did decide to require development of additional data to fully characterize the oncogenic risk of daminozide and UDMH before making any further regulatory decisions. In February 1986, the Agency imposed extensive data requirements on daminozide registrants under section 3(c)(2)(B) of FIFRA. The required data included additional oncogenicity studies, mutagenicity data, plant and animal metabolism studies, livestock feeding data, crop field trials, degradation in food data, storage stability information, market basket surveys, and development of refined, more sensitive detection methodologies.

In the interim period while data were being generated, the Agency determined that certain changes to daminozide registrations intended to reduce human exposure were appropriate. These included: reduced label application rates for apples and limitation of the use on grapes to Concord grapes (not for use as raisins). In addition, the Agency established a lower apple tolerance with a specific expiration date.

By the end of December 1988, much of the required data had been received and reviewed by the Agency. As a result of the review of these data, in particular a 12-month interim sacrifice report of a UDMH oncogenicity study in mice, the Agency has preliminarily determined that dietary exposure to UDMH represents a significant carcinogenic risk which outweighs the benefits of use of daminozide on food crops and therefore warrants the cancellation of the food uses of daminozide. The carcinogenic risk posed by non-dietary exposure to daminozide and UDMH do not outweigh the benefits and are not significant enough to take cancellation action. Therefore, the Agency is proposing that non-food uses be continued without modification of the terms and conditions of registrations.

The Agency has recently evaluated the new Uniroyal data in conjunction with the previously considered (historical) data on daminozide and UDMH in a weight-of-the-evidence determination. Based on this evaluation both daminozide and UDMH were classified as B2 chemicals, probable human carcinogens. In both the historical studies (NCI 1978; Toth 1977), judged inadequate for risk assessment by the SAP in 1985 and the new Uniroyal studies, daminozide produced vascular and lung tumors in mice. In the more recent Uniroyal mouse study, daminozide showed a statistically significant increase in hemangiomas/ hemangiosarcomas with increasing dose (Cochran Armitage trend analysis), but not by pairwise comparison (Fisher's exact test - a statistical comparison of control and treated animals). A dose-related trend for lung tumors was also seen in male mice. The Agency believes the new data supported by the occurrence of similar tumors in the historical data are sufficient to classify daminozide as a probable human carcinogen. However, the Agency also believes the oncogenic response seen in the daminozide studies is likely caused by the presence of UDMH in the test material and/or metabolic conversion to UDMH.

Vascular and lung tumors seen in the historical UDMH data were also seen in the one-year interim sacrifice in mice from the new Uniroyal study at 80 and 40 ppm. The increase in vascular tumors at 80 ppm was statistically significant by pairwise comparison and trend analysis. UDMH has produced a clear oncogenic response in mice at the highest dose tested and the Agency anticipates that an increase in vascular tumors will also be seen at the lower dose at terminal sacrifice (the 40 ppm dose showed one hemangioma in both a male and female mouse at the one year interim sacrifice).

Neither the Uniroyal rat studies in daminozide (completed) and UDMH (one-year interim sacrifice) or the historical rat data produced treatment related lung or vascular tumors in feeding studies.

The Agency has used data from a 1986 market basket survey, recent crop field trial data, and recently conducted animal feeding studies to estimate exposure for both daminozide and UDMH. From the interim sacrifice report of the UDMH mouse cancer study, the Agency calculated an interim carcinogenic potency factor based on the incidence of hemangiosarcomas (malignant vascular tumors) and combined hemangiomas/hemangiosarcomas of the liver. Based upon this information, the Agency has estimated the lifetime risk of cancer for the general population due to dietary exposure to UDMH to be 4×10^{-5} (5×10^{-5} if an estimate of metabolic conversion of daminozide to UDMH in the gut is considered). (The lifetime risk to the general population [4×10^{-5}] is somewhat lower than the risk cited in the Apple Tolerance Extension document of January 31, 1989 [54 FR 6392] because of a slight overestimate of dietary exposure made in the tolerance document.) The Agency is particularly concerned that a disproportionate share of the lifetime risk occurs from childhood exposure because of the high ratio of food intake per unit bodyweight and the relatively high proportion of a child's diet that is composed of foods which may contain daminozide and UDMH residues. The annual lifetime risk to non-nursing infants (0 to 1 year of age), the highest exposure group, from one year exposure to UDMH is estimated to be approximately 5×10^{-6} (6×10^{-6} if 1 percent metabolic conversion is assumed). The Agency has sought the advice of the National Academy of Science (NAS) as to whether relatively high exposure during infancy and childhood make a person more susceptible to cancer later in life.

The benefits from daminozide use have been assessed in terms of economic impacts which would result if the registered uses of daminozide were cancelled. In assessing benefits, the Agency considered uage information from 1985 and 1988. The Agency concluded the overall impacts from cancellation of daminozide on food uses would be insignificant to minor. Although there are alternatives for some of daminozide's uses, no one alternative chemical provides all the benefits of daminozide. For food uses, the greatest anticipated annual impacts would be in apple production. Estimates of the economic impact on the apple industry are based on 10 percent of the crop treated. Earlier estimates made in conjunction with the apple tolerance extension document of January 31, 1989, referenced a 4 to 8 percent annual crop treatment. The higher estimate (5 to 10 percent) in this document is a result of additional and more in-depth information gathered in the last two months.

Based on 1988 usage data, impacts on the apple use, in terms of net social cost for the whole of society, could range from $18 - 81 million with the most likely impact approaching the lower end of this range. rowers of Stayman and McIntosh varieties would suffer the greatest individual impact. For other food uses, the annual impacts are anticipated to be approximately $1.5 - 5.5 million for peaches, approximately $260,000 for peanuts, and negligible impacts for nectarines, cherries, grapes, and pears. The Agency needs additional information regarding the benefits of daminozide use on tomato transplants and is requesting this information in this document.

The Agency considered a number of options to further reduce dietary exposure and thus reduce carcinogenic risk. In particular, limiting use to certain crops and varieties was considered. None of the considered options was found to reduce the cancer risk such that benefits outweighed risks. Therefore, since the risks of continued use outweigh the benefits, EPA is proposing cancellation of all food uses.

The Agency also considered an emergency suspension of daminozide use on food crops. Although EPA believes that the available data are a cause for concern, the level of risk during the time necessary to complete a cancellation action is not unreasonably high. Also, exposure is expected to decrease as a result of declining use which will further reduce risk.

The Agency has also examined the risks and benefits of non-dietary exposure. The Agency estimated that the greatest individual lifetime cancer risks posed by non-dietary exposure to UDMH from use on greenhouse ornamentals is 1×10^{-6}. In addition, the Agency believes that annual grower and consumer losses (as high as $4.7 million in an industry with an annual wholesale value of $78.5 to $104.5 million) would be substantial if the uses of daminozide on ornamentals and bedding plants were cancelled. In this case, the Agency believes that the benefits outweigh the risks for non-dietary use of daminozide on ornamentals and bedding plants. The Agency is proposing that all registrations for use on ornamentals and bedding plants be retained without modifications to the label.

The Agency will also be proposing in the near future the revocation of daminozide tolerances for all raw agricultural commodities as well as the daminozide food and feed additive regulations for processed commodities. No separate tolerances or food and feed additive regulations have been established for UDMH. As noted above, the Agency established a lower tolerance for daminozide on apples with an expiration date while data were being generated. On January 31, 1989 (54 FR 6392; February 10, 1989), the apple tolerance was extended for an additional 18 months to allow the Agency time to complete the Special Review of daminozide.

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I. **INTRODUCTION**

A. General Background and Organization

This document summarizes the data and information utilized by the Environmental Protection Agency (EPA) in its evaluation of the risks and benefits of the registered uses of the plant growth regulator daminozide (trade name Alar). Daminozide's principal use is on apples, although it is used on other food commodities as well as certain ornamental plants.

This Technical Support Document addresses the risks and benefits of daminozide use and is comprised of five parts. Part I is this introductory section. Part II evaluates the potential risks associated with daminozide use, including: descriptions and evaluations of the risk evidence, exposure data, and the Agency risk assessments. Part III estimates and summarizes the economic benefits associated with daminozide use. Part IV presents the various regulatory options considered by the Agency in its risk/benefit decision and describes the Agency's regulatory decision for each use of daminozide. Part V is the bibliography of references upon which the Agency relied in making its regulatory decision.

B. Legal Background

A pesticide product may be sold or distributed in the United States only if it is registered or exempt from registration under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) as amended (7 U.S.C. 136 et seq.). Before a product can be registered it must be shown that it can be used without "unreasonable adverse effects on the environment" (FIFRA section 3(c)(5)), that is, without causing "any unreasonable risk to man or the environment, taking into account the economic, social, and environmental costs and benefits of the use of the pesticide" (FIFRA section 2(bb)). The burden of proving that a pesticide meets this standard for registration is, at all times, on the proponent of initial or continued registration. If at any time the Agency determines that a pesticide no longer meets this standard for registration, then the Administrator may cancel this registration under section 6 of FIFRA.

The Special Review process, formerly called the Rebuttable Presumption Against Registration (RPAR) process, is a mechanism by which the Agency collects and evaluates information on the risks and benefits associated with the uses of pesticides to determine whether any use causes unreasonable adverse effects to human health or the environment. The Special Review process is currently governed by 40 CFR Part 154. At the time of initiation of the daminozide Special Review, the Special Review process was governed by 40 CFR Part 162.

Through the Special Review process the Agency (1) announces and describes the Agency's risk concerns regarding pesticidal use based on certain risk criteria, (2) establishes a public docket, (3) proposes a regulatory decision, (4) solicits comments from the public on the proposed decision and issues concerning the Special Review, (5) responds to significant comments from the public, the Secretary of Agriculture and the Scientific Advisory Panel, and (6) makes a final regulatory decision based on a balancing of risks and benefits associated with a pesticide's use.

Pursuant to 40 CFR 154.31, the Administrator is required to prepare a Notice of Preliminary Determination stating which uses of a pesticide product satisfy the risk criteria set forth in 40 CFR 154.7. At the time of the initiation of the Special Review of daminozide the risk criterion for oncogenic effects was set forth at 40 CFR 162.11(a)(3)(ii)(A).

In determining whether the use of a pesticide poses risks which are greater than the benefits, in addition to total cancellation the Agency considers possible changes to the terms and conditions of registration which can reduce risks, and the impacts of such modifications on the benefits of use. If the Agency determines that such changes sufficiently reduce risks to the level where the benefits outweigh the risks, it may conclude the Special Review process by requiring such changes. Unless the Agency determines that the basis of the Special Review has been rebutted, it will issue a Notice of Intent to Cancel pursuant to section 6(b) of FIFRA. The Notice of Intent to Cancel may specify changes in the terms of the registration which the Agency considers sufficient to avoid cancellation.

Issuance of the Preliminary Notice of Intent to Cancel accompanying this Technical Support Document means that the Agency has assessed the potential adverse effects associated with the use of daminozide and preliminarily determined that the risk criterion for oncogenic effects set forth in 40 CFR 154.7(a)(2) has been satisfied and that these risks exceed the benefits for all food uses of daminozide.

C. Chemical Background

Daminozide is the active ingredient of Alar, Kylar, and B-Nine, formulated products produced by Uniroyal Chemical Company, Inc. Daminozide products are formulated by reacting succinic anhydride with 1,1 (unsymmetrical)-dimethylhydrazine (UDMH) to make succinic acid dimethyl hydrazine (SADH) (The Pesticide Manual, 1979). Although daminozide is the parent compound and active ingredient in Alar products, UDMH is also present as a degradate and metabolite of daminozide. It is a contaminant in both technical and formulated products; products can form additional UDMH through hydrolysis. Formation of UDMH by hydrolysis increases as a function of time and increasing temperature. For example, the formation of UDMH from daminozide residues is known to occur following the boiling and/or cooking of apples. Metabolism data have shown that daminozide hydrolyzes to UDMH in the mammalian body.

D. Regulatory History of Daminozide

1. Uses

Daminozide is a plant regulator used in controlling vegetative and reproductive growth of orchard crops including apples, cherries, nectarines, peaches, and pears and other crops including peanuts, grapes, tomatoes, and ornamentals. Specifically, on apples, daminozide's major use, it can affect flower bud initiation, fruit set and maturity, preharvest fruit drop and the market quality of fruit at harvest and during storage. Daminozide can hasten and concentrate ripening of peaches, sweet and tart cherries, and nectarines. On grapes, it can increase fruit set. Daminozide can also retard stem elongation on tomato transplants. On peanuts, daminozide can produce shorter, more erect peanut vines and can increase yields. The use of daminozide on ornamental plants can produce shorter, more compact growth on chrysanthemums, azaleas, hydrangeas, and bedding plants.

This chemical is registered as an 85 percent water soluble dry concentrate formulation. The amount of daminozide that is applied as a field spray ranges from 0.9 to 6.9 pounds active ingredient per acre per year, depending on the crop, time of application, and desired effects.

2. Regulatory History

Daminozide was first registered in 1963 by the Uniroyal Chemical Co., Inc. for use on potted chrysanthemums. In 1968, daminozide was first registered for food use (apples) and was later registered for use on several other raw agricultural commodities.

A variety of tolerances, which are the maximum permissible residue levels allowed on raw agricultural commodities or as secondary residues such as those found in meat, milk, and eggs, have been established for daminozide. In instances where pesticides concentrate during processing, food and feed additive regulations have also been established. Tolerances were first established for daminozide on apples in 1968 and later established for daminozide on peanuts and other commodities. Tolerances for daminozide in or on raw agricultural commodities, processed foods, and animal feeds are listed in 40 CFR §180.246,

§185.1550 and §186.1550. There are no separate tolerances established for residues of UDMH. The established daminozide tolerances are presented in Table 1.

TABLE 1.

DAMINOZIDE TOLERANCES

COMMODITY	TOLERANCE
Apples	20 ppm *
Grapes	10 ppm
Sweet cherries	30 ppm
Sour cherries	55 ppm
Peaches	30 ppm
Peanuts	30 ppm
Peanut hay	20 ppm
Peanut hulls	10 ppm
Nectarines	30 ppm
Pears	20 ppm
Poultry, kidney	2.0 ppm
Eggs	0.2 ppm
Meat (inc. fat and meat byproducts of cattle, goats, hogs, horses, sheep and poultry (except kidney))	0.2 ppm
Milk	0.02 ppm
Tomatoes	0.5 ppm
Concentrated tomato products	3.0 ppm
Dried tomato pomace	10 ppm
Peanut meal	90 ppm

* = Tolerance set to expire July 31, 1990.

During the 1970's, four chronic oncogenicity studies were conducted, two studies with daminozide and two studies with UDMH, that suggested a potential basis for concern (Toth, 1973; Toth, 1977a; Toth, 1977b; NCI, 1978). However, these studies had deficiencies in study design (only one dose level was tested and concurrent controls were not used in the Toth studies), record keeping (laboratory notebooks were not maintained), and study documentation that limited their usefulness for cancer risk assessment.

In the early 1980's, the Agency decided to review daminozide through its Registration Standard process and identify outstanding data gaps. This process was completed in 1984 and a Registration Standard was issued in June of that year. Prior to the completion of the Registration Standard, in August 1983, the Agency issued a Data Call In Notice (DCI) under section 3(c)(2)(B) of FIFRA requiring the registrants to generate certain metabolism and feeding study data. In the Registration Standard, the Agency expressed its cancer risk concern about daminozide and UDMH and included a second DCI that required additional data not asked for in the August 1983 DCI.

On July 18, 1984, EPA issued a Notice of Special Review of daminozide products (49 FR 29186) and a Position Document 1 or PD 1, which set forth the scientific rationale for the Agency's action. This action was based on the Agency finding that pesticide products containing daminozide met the 40 CFR 162.11(a)(3)(ii)(A) (now 40 CFR 154.7(a)(2)(i)) risk criterion relating to oncogenicity. That section provided that a Special Review shall be conducted if the use of a pesticide "induces oncogenic effects in experimental mammalian species or in man as a result of oral, inhalation or dermal exposure...." The Agency decided to proceed with a cancellation action based on cancer risk concerns, despite the limited nature of the cancer data base, because it believed that all four relevant studies, plus a 1984 inhalation study conducted by the U.S. Air Force (Haun, 1984), were sufficient when considered together to warrant a Special Review of the food uses. In addition to causing oncogenic effects in laboratory animals, UDMH also appeared to be mutagenic in both the presence and absence of metabolic activity (Rogers and Back, 1981). (The Agency has since received additional data on the mutagenic potential of UDMH which report negative activity. However, based on the overall weight-of-the-evidence, the Agency concluded UDMH presents a mutagenicity concern and supports an oncogenicity concern for UDMH and daminozide.)

Because of the level of concern about dietary exposure, particularly to young children, the Agency developed a combined Preliminary and Final Determination and Draft Cancellation Notice, which included a Draft PD 2/3/4, in September 1985. The

Draft PD 2/3/4 and Cancellation Notice were submitted to the Scientific Advisory Panel (SAP) and USDA as required by FIFRA. The SAP was established by Congress to provide scientific review of pesticide actions taken by the Agency. The SAP believed that the data from these studies were insufficient to support a quantitative risk assessment for either daminozide or UDMH because of various limitations in methodology and documentation. Although EPA is not bound by SAP's opinion, the Panel's view is an integral part of the Agency's Special Review decisions. Therefore, based in large part on the SAP's review of the data base for daminozide and UDMH, EPA decided to reassess its position and, in particular, its reliance on the existing cancer studies as the basis for its cancellation action.

EPA concluded that it would not proceed with the cancellation action at that time, but instead would take other steps to protect public health and require Uniroyal to conduct a wide range of testing that would enable EPA to base its risk assessment on a more complete and sound scientific data base. In addition to requiring data, the Agency determined that certain changes to daminozide registrations intended to reduce exposure were appropriate. These included:

(1) discontinance of the use of daminozide on grapes intended for raisins;

(2) labelling new products for use only on Concord-like grapes (grapes not intended for raisins);

(3) reducing application rates on apple trees from 8 lbs/acre to 4 lbs/acre for Spring treatment and 8 lbs/acre to 3 lbs/acre for the later treatment;

(4) inclusion by Uniroyal of a use advisory in every bag of ALAR 85 cautioning against the use of daminozide on apples meant for use in apple sauce and juice; and

The Agency also lowered the tolerance for residues of daminozide in or on the raw commodity apples from 30 parts per million (ppm) to 20 ppm (51 FR 12889); the Agency set an expiration date of July 31, 1987 for the reduced apple tolerance since it believed that some of the residue and market basket survey data would be completed by then and a further evaluation of the tolerance could be undertaken.

The new data required in 1986 under section 3(c)(2)(B) included a two-year drinking water oncogenicity study on UDMH using mice and rats. (A two-year feeding study on daminozide using mice and rats had already been started as a result of the DCI issued with the Registration Standard.) Uniroyal was required to perform interim sacrifices at eight and twelve months on the UDMH studies, with the possibility that regulatory action could be taken on the basis of these interim data, rather than waiting until the studies were finished. In addition to oncogenicity studies, the Agency also required extensive other data submissions including mutagenicity data, plant and animal metabolism studies, livestock feeding data, crop field trials, degradation in food data, storage stability information, market basket surveys, and analytical methods.

In another action, on July 1, 1986, the Natural Resources Defence Council (NRDC), Public Citizen, the State of New York, the State of Maine, and others petitioned the Agency to amend the raw agricultural commodity tolerance for daminozide residues on apples and establish the tolerance at zero. In denying the petition on January 6, 1987, the Agency noted that it did not have adequate data to determine whether the long term presence of daminozide residues in foods posed a health hazard to the U.S. population. On March 9, 1987, NRDC and the other petitioners sued the Agency seeking review of the denial of their petition. The Ninth Circuit Court of Appeals dismissed the suit for lack of jurisdiction in Fall of 1988. The Court held that the denial of a citizen petition under Section 408 was not subject to an initial appeal in the Court of Appeals and that denial of such a petition under Section 409 was only appealable to the Court of Appeals following a petitioner's exhaustion of its right to make objections to and request a hearing before the Agency. NRDC asked the Supreme Court to review this Decision, but in April, 1989, the Supreme Court decided not to hear the case.

Residue data available in 1987 did not indicate that the apple tolerance could be lowered below 20 ppm without some legally treated apples being over tolerance. In addition, the Agency did not have sufficient toxicology data to determine if a new permanent tolerance would adequately protect public health. The 20 ppm tolerance was therefore extended until January 31, 1989, at which time toxicology data (primarily interim sacrifice data) would be available for use in the apple tolerance assessment. On January 31, 1989, the Agency announced that it would seek cancellation of all daminozide food uses. Because the Agency coordinates its actions affecting tolerances for pesticides with its actions regarding corresponding registrations of pesticides, and because EPA concluded that it would not be appropriate to issue an emergency order suspending daminozide registrations, EPA also extended the apple tolerance (54 FR 6392) for an additional 18 months to allow adequate time to complete anticipated cancellation proceedings. The Agency determined that the carcinogenic risk to the general U.S. population for the 18 month period was insufficient to warrant a change in the existing temporary tolerance.

The majority of the data required in 1986 and earlier have been received and have been reviewed.

D. Analysis of PD 1 Rebuttal Comments

After issuing the PD 1, the Agency received numerous rebuttal comments during the allowed comment period concerning the oncogenic basis for Special Review and the data used to estimate dietary exposure. Major comments were submitted by Uniroyal Chemical Co., the Washington State Horticultural Association, the Natural Resources Defense Council, and the National Coalition Against the Misuse of Pesticides. The rebuttal comments were addressed by the Agency in the Draft PD 2/3/4.

The majority of these comments addressed the risk assessment performed by the Agency for daminozide and UDMH and the validity of the studies used to perform the assessments. The cancellation action that is now being proposed is primarily based on new data received in the last several months. Accordingly, the Agency has not addressed the prior comments on the earlier data base beyond the response contained in the Draft PD 2/3/4. The Draft PD 2/3/4 is available in the public docket. The Agency believes the estimates of risk, based on the new data, are more appropriate for regulatory purposes and thus should be the focus of public attention and comment.

II. RISK ASSESSMENT

This portion of the Technical Support Document is divided into two sections. The first section is Hazard Identification and addresses qualitatively the adverse effects associated with daminozide/UDMH exposure and other relevant data necessary to estimate risk, including dose response assessment, determination of the most appropriate cancer potency values, evaluation of the weight-of-the-evidence and subsequent cancer classification of daminozide/UDMH. The second section discusses exposure and estimates risk.

A. Hazard Identification

1. Oncogenic effects

Based on information available to date, the Agency has determined that the adverse effect of primary concern associated with daminozide/UDMH exposure is carcinogenicity.

a. Historical data base for daminozide/UDMH

Several carcinogenicity studies serve as the historical basis of concern about the carcinogenic potential of daminozide and UDMH. These studies, which were summarized in the daminozide PD 1 and Registration Standard, suggested that daminozide is oncogenic in laboratory rats and mice, and UDMH is oncogenic in laboratory mice and hamsters (NCI, 1978; Toth, 1977a; Toth, 1977b; Toth, 1973; Haun, 1984).

One study indicated that administration of daminozide in feed caused endometrial adenocarcinomas and leiomyosarcomas of the uterus in female rats (rare sites for tumor formation); also hepatocellular carcinomas were formed in male mice, and alveolar/bronchiolar carcinomas and adenomas were formed in male and female mice (NCI, 1978). In a second study, administration of daminozide in drinking water resulted in a statistically significant increase in the incidence of blood vessel tumors (a rare site for tumor formation) and lung tumors in both male and female mice, as well as a statistically significant increase in the incidence of kidney tumors in male mice (Toth, 1977a). Analysis of the drinking water in this latter study indicated that the hydrolysis product, UDMH, increased as a function of time. In a third study, administration of drinking water containing UDMH resulted in a statistically significant increase in the incidence of blood vessel tumors and lung tumors in both male and female mice (Toth, 1973). Formation of kidney and liver tumors were also noted in this study. In addition, colon tumors have been reported from the administration of UDMH in the drinking water of hamsters (Toth, 1977b). In another study performed by Haun et al. (Haun, 1984), the effects of inhalation exposure to UDMH were tested on both rats and mice. Increased incidences of pulmonary bronchiolar adenomas/carcinomas occurred in male Fischer 344 rats and pancreatic islet cell adenomas and carcinomas occurred in all treated groups of males. Vascular angiomas/angiosarcomas and liver adenomas occurred in female C57BL/6 mice. These studies were discussed in greater detail in the PD 1 issued on July 18, 1984 (49 FR 29186) and in the Draft PD 2/3/4, issued in September 1985.

b. Recently received daminozide data

In response to the DCI issued with the 1984 Registration Standard, additional oncogenicity studies with daminozide in the rat and mouse were submitted on August 31, 1988. In one oncogenicity study (Uniroyal, 1988a), groups of CD-1 mice (50 sex/group) were administered technical daminozide in the diet for two years at 0, 300, 3000, 6000, and 10,000 ppm. Review of the daminozide mouse study indicates that there is a statistically significant increase in hemangiosarcomas and combined hemangiomas/hemangiosarcomas (malignant and benign blood vessel tumors, respectively) with increasing dose (Cochran Armitage trend test - a statistical recognition of a positive increase in tumors with increasing dose) but not by pairwise comparison (Fisher Exact test - statistical comparison of the control and treated groups). In addition, combined benign and malignant alveolar/bronchiolar tumors had a dose-related trend in male mice and a significant pairwise difference between the 6000 ppm dose group and the controls in males and females.

A review of the tumors noted in the study is shown in Table 2 and indicates that the major tissue/organ system affected by daminozide is the vascular system of the liver.

Table 2.

DAMINOZIDE (CD-1) MOUSE STUDY
INCIDENCE OF BLOOD VESSEL TUMORS OF THE LIVER [ab]

	DOSAGE LEVELS (ppm)				
	0	300	3,000	6,000	10,000
Males					
Hemangiomas	2/50(4)[+] p=0.292	0/50(0) p=0.247	2/50(4) p=0.691	1/50(2) p=0.500	2/48(4) p=0.676
Hemangiosarcomas	4/50(8)* p=0.008	1/50(2) p=0.181	1/50(2) p=0.181	2/50(4) p=0.339	8/48(17) p=0.159
COMBINED INCIDENCE	6/50(12)* p=0.010	1/50(2) p=0.056	3/50(6) p=0.243	3/50(6) p=0.243	10/48(21) p=0.182
Females					
Hemangiomas	2/46(4) p=0.472	0/49(0) p=0.232	1/49(2) p=0.476	1/47(2) p=0.492	1/50(2) p=0.468
Hemangiosarcomas	2/46(4)** p=0.019	1/49(2) p=0.476	1/49(2) p=0.476	0/47(0) p=0.242	6/50(12) p=0.163
COMBINED INCIDENCE	4/46(9)** p=0.048	1/49(2) p=0.162	2/49(4) p=0.309	1/47(2) p=0.174	7/50(14) p=0.312

a Source: October 24, 1988 EPA memorandum from C.J. Nelson based on data from Uniroyal, 1988a.

b rate= number of tumor bearing animals/number of animals at risk.

+ = the number in parentheses indicates the percentage incidence.

NOTE: Significance of trend denoted at control.
* denotes $p < 0.01$
** denotes $p < 0.05$

The increase in hemangiomas/hemangiosarcomas at the high dose in male and female mice is considered to be related to treatment with daminozide for the following reasons: (1) Tumors at the high dose (10,000 ppm) are nearly twice those of the concurrent controls. (2) The incidence of hemangiosarcomas at the high dose is outside of the historical control range for this tumor type in this strain of mouse. The historical control range for hemangiosarcomas is 0 (zero) to 2.0 percent (mean 0.5 percent) for males and 0 (zero) percent for females in the four feeding studies performed at the same laboratory as the daminozide study and discussed below (Uniroyal, 1988b; Uniroyal, 1988c; Uniroyal, 1988d; and Uniroyal, 1988e). Hemangiosarcomas would be considered uncommon tumors (<1.0 percent) based on these ranges in the CD-1 mouse. (3) The incidence of hemangiosarcomas in the control groups is also outside the historical control range for this tumor type. An explanation for this is not readily apparent but these results raise a question about the adequacy of the control groups, especially since the incidence in male mice in the two lowest dosage groups was within the historical control range. An independent review of the pathology slides was required by the Agency and confirmed the incidence of tumors in control animals (EPL, 1988). (If the incidence of blood vessel tumors in the controls had fallen within the historical control range, it is possible that the increased incidence in higher doses would have been statistically significant by pairwise comparison.) (4) Hemangiomas/hemangiosarcomas are the same tumor types which were noted in the cancer studies serving as the basis for initiation of the Special Review and the ongoing oncogenicity studies on UDMH which are discussed below.

In the other daminozide cancer study submitted by Uniroyal (Uniroyal, 1988b), groups of Fischer 344 rats (50 sex/group) were fed daminozide at 0, 100, 500, 5000 and 10,000 ppm. A review of this rat study shows no evidence of treatment-related oncogenicity. Treated animals showed no statistically significant increase in tumors by either the Cochran Armitage trend analysis or by pairwise comparison using the Fisher's exact test.

c. Recently received UDMH data

In addition to oncogenicity feeding studies with daminozide, Uniroyal is currently conducting 2-year UDMH drinking water oncogenicity studies in the rat (Fischer 344) and mouse (CD-1). The Agency required that Uniroyal submit interim sacrifice reports from the mouse and rat studies in order to better characterize the formation of tumors and serve as a basis for regulatory action if the data warrant.

In one study (Uniroyal, 1988c), groups of Fischer 344 rats (70 sex/dose) are being administered UDMH in drinking water at 0, 1, 50, and 100 ppm for two years. The one-year interim sacrifice (20 animals per sex/dose) data have been submitted and reviewed by the Agency. Although there was a dose-related increase in the incidence of corneal opacity in all female treated groups, there was no significant difference in the incidence of tumors in any dose group when compared to controls.

The CD-1 mouse is currently being tested for oncogenic effects in two separate studies at several dosage levels. In the "low dose" mouse study (Uniroyal, 1988d), UDMH was administered in water using doses of 0, 1, 5, and 10 ppm UDMH in males and 0, 1, 5, and 20 ppm in females. The test used 90 animals per sex per dose. Fifty animals per sex per dose were dosed for two years. Twenty animals were sacrificed at eight months and 12 months from the initiation of the study. Although at eight months some toxicity was observed in the liver, no apparent increase in tumors was seen. The liver toxicity noted was in the form of brown pigment and hypertrophy of the liver in males at the highest dose. The 12-month report did not show a significant increase in tumor formation when comparing treated animals to controls. The terminal sacrifice of this study occurred in January 1989 and the final report of this study is due in September 1989.

On March 19, 1987, EPA required Uniroyal to perform an additional oncogenicity study in mice. This action was taken because the Agency did not believe the maximum tolerated dose (MTD) would be achieved in the CD-1 mouse oncogenicity study with high doses of only 10 - 20 ppm. [Both the EPA "Guidelines for Carcinogen Risk Assessment" (51 FR 33992 at 33995) and the Office of Science and Technology Policy (OSTP) guidance for federal carcinogenic risk assessment (50 FR 10372 at 10413) stress the importance of the MTD to the interpretation of the study. The OSTP guidance defines MTD, usually the highest dose tested, as the dose "which, when given for the duration of the chronic study, is just high enough to elicit signs of minimal toxicity without significantly altering the animal's normal life span due to effects other than carcinogenicity.....The purpose of using the MTD is to provide maximum opportunity for the detection of a neoplastic response." If no tumors are produced at the MTD, it is reasonable to conclude that any regulatory action necessary to protect against the other forms of toxicity will also protect against any potential carcinogenicity.] Uniroyal believed that the results of a 13-week subchronic study (Cranmer, M. and Frith, C., 1987) supported 20 ppm as the MTD for mice and that elevating the dose would threaten the lives of the animals and the validity of the study. Uniroyal's opinion was based on: (1) microscopic examination of liver, spleen and bone marrow which they believe suggests significant cellular alterations, (2) evaluation of hematological effects from which they suggested significant changes had occurred to critical blood elements resulting in life-threatening anemia, and (3) changes in alkaline phosphatase levels which they considered to be significant and which they correlate with histopathological changes in the liver. The Agency considered this interpretation of the 13-week data but was not satisfied that the changes noted in the report were biologically meaningful. The Agency was of the opinion that the effects reported by Uniroyal were not life-threatening in nature. EPA believed that higher doses were necessary and required the additional carcinogenicity study at 0, 40, and 80 ppm dose levels.

The second study in the CD-1 mouse is currently underway (Uniroyal, 1988e). Groups of 90/sex/dose are being administered UDMH in drinking water at 0, 40, and 80 ppm. As with the low dose study, 20/sex/dose were sacrificed at 8 and 12 months. The 8-month interim sacrifice report noted hematological effects (dose-related decreases in erythrocyte count, hematocrit, and hemoglobin levels when compared to controls) in high dose males, accentuation of liver lobulation in both dosage groups of males, liver cell hypertrophy, single cell necrosis and bile pigment accumulation in liver of treated males as well as increased bile pigment accumulation in the females. Increases in benign lung tumors (alveolar/bronchiolar adenomas) in both sexes were reported at 80 ppm.

The 12-month interim sacrifice report showed the same toxicity effects at the same dose levels as reported in the 8-month sacrifice (liver lobulation, single cell necrosis, etc., in the males). In addition to these effects, there was an increased incidence of vascular tumors of the liver in male and female mice and an increased incidence of alveolar/bronchiolar tumors in the lungs of male and female mice. The incidence of vascular liver tumors is noted in Table 3 and the incidence of benign lung tumors is presented in Table 4. The terminal sacrifice for this study is scheduled for mid-May 1989 and the final report is due to EPA in January 1990.

As discussed in the risk characterization section (III.C.), the cancer risk assessment and the basis for Agency regulatory action is the malignant blood vessel tumor response seen at the 80 ppm UDMH dose level in male and female mice at one year.

Table 3.

INTERIM RESULTS FROM UDMH (CD-1) MOUSE STUDY INCIDENCE OF BLOOD VESSEL TUMOR RATES [ab]

	DOSAGE LEVELS (ppm)		
Tumor Type	0	40	80
Males			
Hemangiomas	0/45(0)+	1/45(2)	2/53(4)
Hemangiosarcomas	0/45(0)**	0/45(0)	9/53(18)**
COMBINED INCIDENCE	0/45(0)**	1/45(2)	11/53(22)**
Females			
Hemangiomas	0/43(0)	1/47(2)	2/51(4)
Hemangiosarcomas	0/43(0)**	0/47(0)	6/51(12)*
COMBINED INCIDENCE	0/43(0)**	1/47(2)	8/51(16)**

a Source: September 9, 1988 EPA memorandum from W.B. Greear based on data from Uniroyal, 1988e.

b rate= number of tumor bearing animals/number of animals examined.

+ = the number in parentheses indicates the percentage incidence.

NOTE: Significance of trend denoted at control. Significance of pairwise comparison with control denoted at dose level. For quantitative risk assessment, these tumor proportions may be amended very slightly due to differences in necropsy interpretation. However, these differences do not affect the estimate of upper bound risk.

* denotes $p<0.05$

** denotes $p<0.01$

Table 4.

INTERIM RESULTS FROM UDMH (CD-1) MOUSE STUDY INCIDENCE OF ALVEOLAR/BRONCHIOLAR TUMOR RATES [ab]

	DOSAGE LEVELS (ppm)		
Tumor Type	0	40	80
Males			
Adenomas	6/45(13)+**	11/45(24)	22/53(41)**
Adenocarcinomas	0/45(0)	0/45(0)	1/53(2)
COMBINED INCIDENCE	6/45(13)**	11/45(24)	23/53(43)**
Females			
Adenomas	4/44(9)**	13/47(30)*	19/51(37)**
Adenocarcinomas	0/44(0)	1/47(2)	0/51(0)
COMBINED INCIDENCE	4/44(9)**	14/47(32)*	19/51(16)**

a Source: September 9, 1988 EPA memorandum from W.B. Greear based on data from Uniroyal, 1988e.

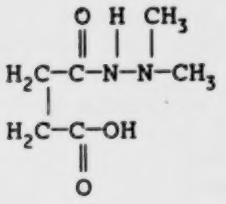
b rate = number of tumor bearing animals/number of animals examined.

+ = the number in parentheses indicates the percentage incidence.

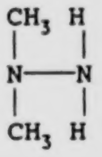
NOTE: Significance of trend denoted at control. Significance of pairwise comparison with control denoted at dose level. For quantitative risk assessment, these tumor proportions may be amended very slightly due to differences in necropsy interpretation. However, these differences do not affect the estimate of upper bound risk.
* denotes $p<0.05$
** denotes $p<0.01$

2. Structure-Activity Relationships

The following are the chemical structures of daminozide and its metabolite, UDMH:



Daminozide



UDMH

Daminozide is a substituted hydrazide compound which is formed by the addition of succinic anhydride to UDMH (1,1 (unsymmetrical)-dimethylhydrazine) to make succinic acid dimethyl hydrazide or SADH. Under various conditions, including those of heating during home food preparation and commercial processing, daminozide is hydrolyzed to UDMH and succinic acid.

The Agency has evaluated several oncogenicity studies on a similarly substituted compound, maleic hydrazide (MH). The Agency issued a PD 1 based on oncogenic concerns (EPA MH PD 1, 1977). However, in the MH PD 2, the Agency noted that the weight-of-the-evidence supporting the MH oncogenicity concern was inconclusive (EPA MH PD 2, 1982). The hydrazines, particularly the substituted forms such as 1,2-dimethyl hydrazine and monomethyl hydrazine, have been reported in open literature to be oncogenic in laboratory animals (IARC, 1974).

The Agency has determined that structure-activity considerations support the conclusion that daminozide and its metabolite, UDMH, have oncogenic potential.

3. Mutagenicity

The mutagenic concerns regarding exposure to daminozide and UDMH are described below and in the daminozide internal peer review document and supporting mutagenicity document (Quest, 1989; Dearfield, 1989).

a. Daminozide

No mutagenic effects were reported in tests using *S. cerevisiae* (Uniroyal, 1983), and the mouse lymphoma cell line (L5178Y) (McGregor, 1988). In another mutagenicity test, daminozide also failed to produce dominant-lethal mutations in a dominant lethal assay in mice (Green et al., 1985). These results tend to indicate that daminozide *per se* is not mutagenic.

b. UDMH

Conflicting results for mutagenicity have been reported in several studies. Uniroyal (Uniroyal, 1988g) has recently submitted reports of several mutagenicity studies which were negative for mutagenic activity. These studies were referenced in the Tolerance Extension Document (54 FR 6392) and included: an Ames *Salmonella* assay for point mutations, a chromosomal aberration assay using Chinese hamster ovary cells, a forward gene mutation assay in Chinese hamster ovary cells, and an unscheduled DNA synthetase assay in primary rat hepatocytes. In addition, negative results have been also reported in mice for induction of micronuclei in bone marrow cells and for sperm abnormalities (Bruce and Heddle, 1979), and dominant lethal mutations in mice (Brusick and Matheson, 1976). Based solely on these studies, there would not be an overt mutagenicity concern.

However, open literature reports of several studies with positive results for UDMH provide a basis for a mutagenicity concern. Tests in which UDMH was positive include reversion to histidine independence in *Salmonella* strain TA 98 (Uniroyal, 1982), differential growth inhibition in wild- type (rec^+) (Suter and Jaeger, 1982), and DNA repair deficient (rec^-) strains of *E. coli* and *B. subtilis* (Suter and Jaeger, 1982), induction of point mutations in *A. nidulans* (Bignami et al., 1981), two mouse lymphoma assays (Rogers and Back, 1981; Brusick and Matheson, 1976), unscheduled DNA synthesis in human lung cells *in vitro* (Brusick and Matheson, 1976), inhibition of mouse testicular DNA synthesis (Seiler, 1977), and DNA damage ("fragmentation") in mouse lung cells *in vivo* (Parodi, 1981). The Agency believes the overall mutagenicity weight-of-the-evidence indicates that UDMH presents a mutagenicity concern and supports an oncogenicity concern for daminozide and UDMH.

4. Metabolism

a. Daminozide

A gavage metabolism study in the rat (Uniroyal, 1984a) indicated that daminozide is excreted in the urine, feces and also as CO_2 as a metabolic breakdown product. After 96 hours, 68.5 percent of the administered dose was found in the feces, 22.7 percent in the urine, and 2.8 percent in the expired CO_2. No metabolites were determined in this study since only the radioactivity of daminozide was followed. About 0.21 percent of the dose remained in various organs including brain, heart, lungs, liver, kidney, and spleen.

In a metabolism study in guinea pigs (Uniroyal, 1984b), the administration of daminozide by gavage resulted in excretion of large amounts of the parent compound, daminozide, and dimethylhydrazine in both the urine and feces. Up to 1.5 percent of the dose was excreted in the urine as UDMH. About 0.42 percent of the administered dose was found in the kidney, 0.30 percent in the lung, and 0.26 percent in the liver.

Most recently, the Agency has received and reviewed results from a metabolism study in miniature swine (Uniroyal, 1987d). This study utilized Charles River miniature swine which were administered approximately 5 mg/kg (approximately 100 ppm) daminozide orally. Analysis of urine indicates that both UDMH and dimethyl nitrosamine (NDMA) were excreted in the urine. After 24 hours, UDMH urine levels ranged from 0.04 to 2.83 ppm (average approximately 1 ppm or 1 percent metabolism of daminozide to UDMH) and NDMA levels ranged from 0.01 to 0.69 ppm. It is assumed that the NDMA observed is the result of UDMH alteration; however, the actual site of metabolic conversion of daminozide to UDMH and NDMA could not be determined. Daminozide was found in almost all tissues, at levels up to 73 ppb, with the liver and kidney containing the highest levels. Although the Agency believes that most of the UDMH and NDMA were excreted in the feces in the first 24 hours, analysis of urine and feces is considered incomplete, because fecal data were not analyzed for the 0 - 24 hour portion of the study. The Agency expects to have these data before issuing the final regulatory determination on daminozide.

The presence of NDMA is a potentially significant finding because NDMA has been shown to be a potent carcinogen in laboratory animals. In 1976, Magee et al. (EPA, 1986) reported that NDMA produced many blood vessel tumors and some parenchymal cell tumors in the livers of rats after oral administration. In addition, Peto et al. (1984) reported that after exposure of groups of male and female Carworth rats to 15 concentrations of NDMA in drinking water (0.033-16.896 ppm), pooled data indicated possible positive trends for tumors of the lung, skin, seminal vesicle, lymphatic/ hematopoietic system, and liver. Liver tumors constituted the only cause of mortality considered to be treatment-related.

b. UDMH

Metabolism studies with UDMH are limited and do not completely characterize UDMH metabolism in mammals. In rats (Mitz, 1962), injections of UDMH resulted in the identification of 50 to 60 percent of the parent compound and two major metabolites (glucose hydrazone and one which was unidentified).

In another rat study (Reed, 1963), UDMH has been found to metabolize to CO_2 for up to 23 percent of the administered dose.

5. Non-Oncogenic Effects

Although not a basis for regulatory action at this time, the non-oncogenic effects of daminozide and UDMH have been reviewed by the Agency and are summarized below.

a. Daminozide

Daminozide has been studied for the determination of its acute toxicity from oral, dermal and inhalation exposures. In one study (Carson, 1963), it was determined that daminozide exhibited an acute toxicity oral LD50 value of 8.4 g/kg body weight in rats (Toxicity Category IV; see 40 CFR 156.10), a dermal LD50 of > 16 g/kg body weight in rabbits, and an inhalation LC50 of > 147 mg/l in rats. A 2-year daminozide study in dogs (Oser, 1966) displayed a no-observed-effect-level (NOEL) equal to or greater than 3000 ppm (75 mg/kg body weight). Toxicity was not reported in this study.

The reproductive effects of daminozide have been investigated in several studies. In one teratology study in Wistar rats (Khera, 1979), doses up to 1000 mg/kg had no adverse maternal, fetotoxic, or teratogenic effects. In a second teratology study in Sprague-Dawley rats (Knickerbocker, 1979), fetotoxicity was observed at 1,800 mg/kg/day. The changes seen in fetuses included excess incidence of missing sternebrae, incomplete ossification of vertebrae, and a reduced incidence of rudimentary ribs. In a three-generation reproduction study in rats (Oser, 1966), one dose level of 300 ppm daminozide (ranging from 13 - 16 mg/kg) was administered to test groups and their progeny. Although no adverse toxic effects were observed, this study did not satisfy Agency requirements because only one dose, which was considered too low for evaluation of compound-related effects, was used.

b. UDMH

UDMH is moderately toxic by the oral route of administration. In one oral toxicity study (NIOSH, 1976), LD50 values for the rat and mouse have been reported as 122 mg/kg and 265 mg/kg, respectively.

6. Human Studies

a. Daminozide

The Agency is unaware of any human studies reporting effects from daminozide exposure.

b. UDMH

As reported in Research and Development Health and Environmental Effects Profile for 1,1-dimethylhydrazine (EPA, 1984):

> Peterson et al. (1970) performed routine physical examinations and laboratory tests, including SGPT (serum glutamate pyruvate transaminase) activity, on Danish Air Force workers who worked with a liquid rocket propellant (1,1-DMH). The concentrations and durations of exposures were not known. It was found that from March, 1961, to January, 1964, SGPT activity was elevated at least once (examinations were performed 3-4 times/year) in 47 (4 percent) of 1123 persons examined. Liver biopsies performed on 26 of these men showed that 6 specimens were pathological (fatty degeneration) and 5 were uncertain, and that all 6 pathological specimens were from patients that had elevated SGPT (levels) at the time of biopsy. There was no follow-up of these workers and it was not possible to confirm that the hepatic effects resulted from exposure to 1,1-DMH, but other conditions known to cause liver damage were ruled out. In an earlier study, positive cephalin flocculation tests were found in five chemical laboratory workers (Shook and Cowart, 1957). The workers were exposed to 1,1-DMH for 6-8 times for no more than 4 hours/week for the subsequent 3 months, but the extent of exposure was not known. Although the above studies suggest that liver damage is a possible effect of exposure to 1,1-DMH in humans, compound related hepatotoxicity cannot definitely be concluded.

7. Weight-of-the-Evidence

The goal of this Weight-of-the-Evidence step of the Cancer Risk Assessment is to reach a qualitative judgment on the carcinogenic potential of daminozide and UDMH.

a. Daminozide

The data available to the Agency at this time indicate that daminozide has produced significant increases in oncogenic responses at multiple sites in both sexes of multiple strains of mice and also in rats. Tumorigenic response also been seen in rats but not in the lung or liver vascular system and the biological significance of these tumors appears to be questionable.

1) Rats

In the recently completed daminozide oncogenicity study in Fischer 344 rats (Uniroyal, 1988b), no oncogenic effects related to exposure to daminozide were observed.

In the NCI study (NCI, 1978), interstitial cell adenomas or carcinomas of the testes occurred in male Fischer 344 rats at both dose levels tested (controls 13/20; 5000 ppm, 46/50; 10,000 ppm 47/50). Although significantly elevated, these tumors also occurred at a high spontaneous rate (182/220) in historical control male rats. In female Fischer 344 rats, uterine endometrial adenocarcinomas occurred at both dose levels (controls, 0/19; 5000 ppm, 5/50; 10,000 ppm, 3/50), and uterine leiomyosarcomas occurred at both dose levels (controls, 0/19; 5000 ppm, 1/50; 10,000 ppm 3/50). The uterine tumors were also of questionable biological significance.

2) Mice

In the recently submitted daminozide mouse (CD-1) oncogenicity study (Uniroyal, 1988a), an increase in both vascular (hemangiosarcomas and hemangiomas/hemangiosarcomas combined) and lung tumors was found. Although the tumor increases were not statistically significant by Fisher's exact test (pairwise comparison), significant dose-related trends were noted for hemangiosarcomas and hemangiomas/hemangiosarcomas combined ($p = 0.01$ for males, $p = 0.048$ for females). In addition, combined benign and malignant alveolar/bronchiolar tumors in male mice had a dose-related trend.

In the NCI study (NCI,1978), pulmonary bronchiolar/alveolar adenomas or carcinomas occurred in female CD-1 mice at both dose levels (controls, 1/20; 5000 ppm, 8/39; 10,000 ppm, 10/48) and liver carcinomas occurred in male mice at both dose levels tested (controls, 0/14; 5000 ppm, 7/50; 10,000 ppm 13/46).

In a daminozide oncogenicity study in Swiss albino mice performed by Toth (Toth, 1977), administration of daminozide in drinking water produced pulmonary bronchiolar/alveolar adenomas or carcinomas and blood vessel tumors (hemangiomas/ hemangiosarcomas) in both male and female mice, as well as renal adenomas in males.

3) Classification

Although deficiencies in the Toth and NCI studies have been noted, it is significant that the studies showed vascular and lung tumors, as found in the recent Uniroyal studies. These studies support the findings in the Uniroyal studies and the Agency believes the weight-of-the-evidence is sufficient to classify daminozide as a B_2 carcinogen, probable human carcinogen. The Agency also believes the oncogenic response seen in the daminozide studies is likely caused by the presence of UDMH in the test material and/or metabolic conversion to UDMH. Table 4a summarizes the weight-of-the-evidence for the potential of daminozide to cause cancer.

b. UDMH

1,1-dimethylhydrazine has been studied for its oncogenicity in multiple species and has produced unequivocal responses in both sexes of mice and hamsters. In these two species an uncommon tumor type, hemangiosarcoma, was found. Additionally, a third species, the rat, was tested using UDMH and exhibited small but significant increases in tumors of the pancreas and bronchiolar adenomas in one study and no oncogenic response in another.

1) Rats

The Agency has received and reviewed the 1 year interim sacrifice report of an oncogenicity study in Fischer 344 rats using doses of 0, 1, 50, and 100 ppm (Uniroyal, 1988c). After 12 months of administration of UDMH, no treatment related increases in tumors were noted.

In an inhalation study performed by Haun et al. (Haun, 1984), pulmonary bronchiolar adenomas/carcinomas occurred in male Fischer 344 rats at the high dose (controls, 2.6 percent; 5 ppm, 5.2 percent), and pancreatic islet cell adenomas and carcinomas occurred in all treated groups of males (controls, 0 percent; 0.05 ppm, 2.2 percent; 0.5 ppm, 7.1 percent; 5 ppm, 5.0 percent). Since this study was performed by the inhalation route of exposure, the Agency believes that it is more appropriate to use the available feeding studies as a basis for quantitative dietary risk assessment. (The label for daminozide products requires applicators to wear masks and, therefore, the Agency considers worker inhalation exposure unlikely.)

2) Mice

The Agency has received and reviewed 1 year interim sacrifice reports on two UDMH oncogenicity studies in mice. Results from these studies indicate that ingestion of UDMH residues for 1 year causes hemangiomas/hemangiosarcomas of the liver in male and female CD-1 mice ($p<0.001$) at the highest dose, as well as alveolar/bronchiolar adenomas in both males and females ($p<0.01$) at the highest dose with significant dose related trends ($p<0.01$). Although these studies are not yet complete, the Agency believes they are sufficient for interim quantitative risk assessment.

In the Haun inhalation study (Haun, 1984), vascular hemangiomas/hemangiosarcomas occurred in female C57BL/6 female mice at the high dose level (controls, 5.2 percent; 5 ppm, 15.2 percent). In addition, liver adenomas occurred in females at the high dose (controls, 2.1 percent; 5 ppm, 11.1 percent). While the Agency believes it is more appropriate to use a dietary cancer study as a basis for dietary risk assessment, it is important to note that the tumors noted in this inhalation study were also seen following oral administration of daminozide to mice (NCI, 1978; Toth, 1973).

In a study performed by Toth (Toth, 1973), Swiss mice administered UDMH developed pulmonary adenomas or carcinomas in males and females. Vascular hemangiomas/hemangiosarcomas also occurred in male and female mice as well as renal adenomas in males. While this study was not used as the basis for the quantitative risk estimates in this document, the study is significant in that the same tumor type is seen to recur due to exposure to daminozide (Toth, 1973).

3) Hamsters

In an oncogenicity study performed by Toth on hamsters (Toth, 1977b), vascular angiomas/angiosarcomas occurred in males (controls, 3 percent; 0.1 percent concentration, 28 percent). In addition, intestinal tumors (cecum) were also noted in both male and female hamsters. The Agency believes that this study is significant because the same tumors (vascular tumors) were also seen in mice (Toth, 1973).

4) Classification

As with daminozide, although deficiencies have been noted in the earlier data (NCI, Toth, Haun), the findings of similar tumor types and sites (liver, vascular, and lung) in both this data and the Uniroyal 1-year interim sacrifice data support a B_2 classification (probable human carcinogen) for UDMH. Table 4a summarizes the weight-of-the-evidence for the potential of UDMH to cause cancer.

Table 4a. NEOPLASTIC RESPONSE REPORTED FOR DAMINOZIDE AND UDMH IN RODENT CARCINOGENICITY STUDIES

Study Name	Species & Route	Tumor Site and Potency (if Calculated)
DAMINOZIDE		
Toth, 1977	Swiss mouse (drinking water)	Blood vessel sarcomas in males and females; alveolar/bronchiolar adenomas and carcinomas in males and females; kidney tumors in males
NCI, 1978a	$B6C3F_1$ mouse (dietary)	Liver carcinomas in males; alveolar/bronchiolar carcinomas and adenomas in males and females
NCI, 1978b	F344 rat (dietary)	Uterine endometrial adenocarcinomas and leiomyosarcomas in females
Uniroyal, 1988a	CD-1 mouse (dietary)	Dose-related trend with regard to blood vessel tumors of liver in males and females; dose-related increase in alveolar/bronchiolar adenomas in males and females; no increases in vascular or lung tumors by pairwise comparison
UDMH		
Toth, 1973	Swiss mouse (drinking water)	Hemangiomas and hemangiosarcomas of liver in males and females; alveolar/bronchiolar adenomas and carcinomas in males and females; kidney and liver tumors in males and females; Q^*_1 estimated to be 8.9 $(mg/kg/day)^{-1}$
Toth, 1977	Hamster (drinking water)	Hemangiomas and hemangiosarsarcomas in males; colon tumors in males and females
Haun, 1984	F344 rat (inhalation)	Pancreatic islet cell adenomas and carcinomas in males; Q^*_1 estimated to be 2.45 $(mg/kg/day)^{-1}$; pulmonary adenomas and carcinomas in males
Haun, 1984	C57BL/6 mouse (inhalation)	Hemangiomas and hemangiosarcomas in females; liver adenomas in females
Uniroyal, 1988e	CD-1 mouse (drinking water)	Blood vessel tumors of the liver in males and females; Q^*_1 estimated to be 0.88 $(mg/kg/day)^{-1}$; alveolar/bronchiolar adenomas in males and females; Q^*_1 estimated to be 2.9 $(mg/kg/day)^{-1}$

8. Dose-Response Assessment

There are two basic components of the dietary risk estimation: cancer potency and exposure through food consumption. Cancer potency is a quantitative measure or estimate of the relationship between exposure to increasing doses of the chemical substance in question and the increased severity (e.g., number of tumors) of the carcinogenic effect. The Agency generally assumes that the dose-response curve for carcinogens in the human population achieves a zero response only at zero dose. As the dose increases above zero, the probability of cancer immediately becomes finite and thereafter increases as a function of the dose received. The carcinogenic risk varies according to the dose-response or cancer potency of the chemical.

The Agency uses a linearized multi-stage model to extrapolate from effects seen at high doses to predict tumor response at low doses. The reason for this is that a very large number of animals need to be tested to determine an effect at a low dose. Animal studies generally do not include a sample size large enough to detect low dose response; therefore, extrapolation is necessary to estimate response at low levels of exposure. Thus, cancer potency is generally extrapolated from responses in high dose animal experiments. Several mathematical models have been developed to extrapolate the potency of carcinogens at low doses from the doses used in animal experiments. The accuracy of the projected cancer potency value at any particular dose is a function of how accurately the mathematical model describes the true relationship between the dose and cancer response when extrapolated to low dose levels.

In the absence of information demonstrating a more appropriate model, EPA usually bases regulatory decisions on the results of cancer assessments based on a linear dose extrapolation model, using the "linearized multi-stage" model. The linearized multi-stage model is based on the biological theory that a single exposure to a carcinogen at a cellular target can initiate an irreversible series of events that eventually lead to a tumor. The Agency's "Guidelines for Carcinogen Risk Assessment" (51 FR 33998) are in concordance with the statement made in 1977 by the National Academy of Sciences (NAS, 1977):

> "... if there is evidence that a particular carcinogen acts by directly causing a mutation in the DNA, it is likely that the dose response curve for carcinogenesis will not show a threshold and will be linear with dose at low doses."

In addition, as stated in EPA's "Guidelines for Carcinogen Risk Assessment":

> "It should be emphasized that the linearized multistage procedure leads to a plausible upper limit to risk that is consistent with some proposed mechanisms of carcinogenesis. Such an estimate, however, does not necessarily give a realistic prediction of risk. The true value of risk is unknown, and may be as low as zero."

Since no statistically significant pairwise increase in tumors was noted by the Fischer exact test in the recently-received daminozide carcinogenicity studies, the Agency based its interim cancer potency estimation (Q^*_1 or the estimated potency per unit exposure) on tumors of the vascular system (combined hemangiomas/hemangiosarcomas) observed in the livers of male and female CD-1 mice after one year of the UDMH study (Uniroyal, 1988e). The data from this study were used for estimation of oncogenic potency for the following reasons: (1) hemangiosarcomas are uncommon malignant tumors and have a low background rate in the strain of mouse used; (2) hemangiosarcomas are the same type of tumors seen in the earlier UDMH and daminozide studies; and (3) since malignant blood vessel tumors have already been noted at the 40 ppm dose level at the one year interim sacrifice, it is very likely that a dose-response relationship will be observed for the occurrence of hemangiomas/hemangiosarcomas by the termination of the UDMH mouse study after two years. In addition, because at this stage the lung tumors have not yet been shown to be outside the normally high incidence of lung tumors in CD-1 mice, for purposes of this document these tumors were not included in the interim potency estimation.

The Q^*_1 for UDMH was estimated using the Crump Global 86 (Howe, 1986) linearized multi-stage model. The interspecies extrapolation for oncogenic effects is accounted for by expressing the dose as mg/squared meter body surface area/day. To modify the rodents' experimental dose to human equivalent dose by surface area assumes that different sized animals are not equally sensitive to equal concentrations. This is based on the observation that smaller animals are often more efficient eliminators of the parent compound and/or its metabolites than larger animals. This difference in elimination ability is accounted for by the difference between the species surface area to volume ratio. To correct for the shorter duration of the study (12 months instead of 24 months), the Druckery correction (Druckery, 1967; Doll, 1971), adjusting the dose by a factor of 0.125, was also used in the calculations. Druckery observed from animal data that the dose (d) and average cancer induction time (T_A) are often approximately related by the formula:

$$dT_A^k = \text{constant}$$

where k may be dependent upon the tumor type. Thus, if an experiment is terminated prematurely, the tumor incidence may be substantially underestimated, because in most cases tumor incidence increases rapidly with age.

Based on the incidences of these vascular tumors at 80 ppm UDMH after one year of treatment, the Agency has calculated an interim cancer potency factor of 0.88 [milligrams/kilogram/day]$^{-1}$ ([mg/kg/day]$^{-1}$). In addition, an interim Q^*_1 of 2.9 [mg/kg/day]$^{-1}$ was calculated on the incidence of lung tumors seen in this same study (Uniroyal, 1988e). As noted above, the Agency has decided to use the interim Q^*_1 calculated on the basis of the increased incidence of blood vessel tumors for the risk assessment in this document.

B. Exposure Assessment

The second major component of cancer risk estimates is exposure. The Agency calculated dietary exposure to daminozide and UDMH for the general population, nursing infants, non-nursing infants, and children aged one to five years, and non-dietary exposure for mixers, loaders, and applicators exposed dermally to daminozide and UDMH.

1. Dietary Exposure

The dietary exposure component of dietary risk consists of two parts. First residue values, or the amount of daminozide and UDMH found or estimated on raw and processed food, were estimated. Second, these residue values were considered in relation to food consumption patterns of differing age groups to determine exposure.

a. Residue Estimates

Daminozide and UDMH residues were determined from (1) market basket survey data, (2) data from controlled field trials conducted in 1986 and 1987, and (3) estimates of residues in meat, milk, eggs, and meat by-products based on livestock feeding studies. The market basket survey data were collected by Uniroyal during three sampling periods in 1986 for the following commodities: raw apples, adult applesauce and juice, baby applesauce and juice, cherry filling, peanuts and peanut butter, and Concord grape juice. Residue values from the market basket survey were assumed to be representative of the total U.S. crop. Residue estimates for the following commodities were based on recent crop field trial data generated by Uniroyal: sweet cherries, grapes, nectarines, peaches, pears, and tomatoes. An estimate of the percent of 1985 crop treated was used with crop field trial data where available. Estimates of daminozide and UDMH residues in meat, milk, eggs, and meat by-products were extrapolated from a feeding study in which animals were dosed with daminozide at levels equivalent to 20 - 200 ppm in feed. In no instance was the tolerance level used in estimating dietary exposure.

For the determination of daminozide residues, the following methods were used: a) "Gas Chromatographic/Mass Spectrometric Determination of Daminozide in High Protein Food Products", J. Assoc. Off. Anal. Chem., Vol. 71, No. 4, p. 735, 1988, or its variations; and b) "Methods of Analysis for ALAR Residue in Various Crops", Pesticide Analytical Manual, Vol. II.

For the determination of UDMH residues, the following methods were used: a) Uniroyal's Method for Determination of 1,1-Dimethylhydrazine in Crops by Isotope Dilution - Mass Spectrometry (unpublished Uniroyal reports, MRID # 410077-01, Accession # 255996); and b) Determination of Residues of Unsymmetrical Dimethylhydrazine in Meat, Milk, and Eggs by GC/MSD (unpublished Uniroyal report, MRID # 402559-01).

i) Market Basket Survey

Uniroyal conducted a series of three market basket surveys during the Spring, Summer, and Fall of 1986 (Uniroyal, 1986; Cheng, 1987). As required by the Agency, Uniroyal collected samples from 72 selected retail grocery stores across the continental United States. Commodities which were sampled included fresh apples (Red Delicious, Golden Delicious, McIntosh, and other varieties), baby apple juice and sauce products, adult apple juice and sauce products, cherry filling, cooked peanuts, peanut butter, and Concord grape juice. Frozen apple samples and unfrozen samples of the other commodities were shipped to two contract laboratories for analysis of daminozide and UDMH levels. The final results of the analyses of all three phases were averaged together and were used in the dietary exposure assessment. The first two sampling periods reflect apples from the 1985 crop while the third sampling period (Fall of 1986) likely reflects apples from the 1986 harvest. The averaged results of the market basket surveys are tabulated in Tables 5 and 6.

Table 5.

AVERAGE DAMINOZIDE RESIDUES FROM THE MARKET BASKET SURVEY [a]

Commodity	Number Sampled	Number of Positives*	Daminozide Average (in ppm)
All apples	254	142	1.0
- Red Delicious	71	39	1.0
- Gold Delicious	69	39	0.7
- McIntosh	45	29	1.1
- Other varieties	69	35	1.3
Baby apple juice	40	28	0.5
Baby apple sauce	40	32	0.5
Adult apple juice	70	62	0.4
Adult apple sauce	70	61	0.4
Cherry filling	70	60	1.5
Cooked peanuts	72	71	0.8
Peanut butter	71	71	0.5
Concord grape juice	48	0	0.02

[a] Source: Uniroyal, 1986.

* = number of samples at or exceeding the limit of detection (0.1 ppm)

Table 6.

AVERAGE UDMH RESIDUES FROM THE MARKET BASKET SURVEY [a]

Commodity	Number Sampled	Number of Positives*	UDMH Average (in ppb)
All apples	173	92	2.6
- Red Delicious	48	20	2.3
- Gold Delicious	47	22	2.1
- McIntosh	33	19	2.2
- Other varieties	45	31	3.9
Baby apple juice	40	33	33.3
Baby apple sauce	40	29	44.0
Adult apple juice	69	65	14.0
Adult apple sauce	70	60	23.9
Cherry filling	70	59	108.1
Cooked peanuts	72	69	24.9
Peanut butter	72	67	10.3
Concord grape juice	47	23	1.5

a Source: Uniroyal, 1986.

* = number of samples at or exceeding the limit of detection of (1 ppb)

ii) Crop field trials

Uniroyal was required to determine the maximum amount of daminozide and UDMH residues which may be contained in raw agricultural commodities resulting from maximum registered application rates and minimum preharvest intervals for crops on labels of registered products. In 1987 and 1988, Uniroyal submitted the required field residue data (Uniroyal, 1987a; Cheng, 1989) for apples, sweet cherries, grapes, nectarines, peaches, peanuts, pears, and tomatoes. Field trial residue data for apples and peanuts were not used in the dietary exposure analysis because the Agency had actual market survey data for those commodities. The mean level of UDMH and daminozide in all commodities tested by Uniroyal in the crop field trials is noted in Table 7.

Table 7.

AVERAGE DAMINOZIDE AND UDMH RESIDUES FROM CROP FIELD TRIALS

Commodity	Number	Daminozide Average (in ppm)	UDMH Average (in ppb)
Apples	39	3.8	6.4
Sweet cherries	17	23.7	18.6
Grapes	13	5.2	34.1
Nectarines	4	14.5	25.0
Peaches	16	11.3	21.3
Peanuts	24	7.7	84.9
Pears	16	8.8	11.9
Tomatoes	16	0.2	1.6

iii) Livestock feeding studies

Daminozide and UDMH residues can occur in meat and milk because apple and peanut by-products left over from processing may be used as cattle and dairy feed. The Agency did not require Uniroyal to measure or sample meat, milk, eggs, and meat by-products in the 1986 Market Basket Survey because residues were not anticipated to be detected in these commodities by the methods available. Use of apple, grape, and tomato pomace and peanut by-products as animal feeds would most likely occur where these crops are grown and processed locally.

Uniroyal submitted the results of two feeding studies, one using goats and the other using laying hens (Uniroyal, 1987b and Uniroyal, 1987c, respectively; Cheng, 1988) to estimate the levels of daminozide and UDMH in meat, meat by-products, milk and eggs.

In the goat study (Uniroyal, 1987b), eleven lactating goats were fed gelatin capsules containing either 0 mg, 50 mg, 150 mg, or 500 mg daminozide per goat per day for 28 days. The corresponding feeding concentrations were estimated to be 0 ppm (or 0 times the anticipated dietary intake), 20 ppm (6.3 x), 60 ppm (19 x), and 200 ppm (63 x) based on an average feed consumption of 2.5 kg per goat.

The following results were noted in the goat study: (1) at the 50 mg/day dose level, daminozide residues of <0.01-0.04 ppm in milk, <0.03 ppm in muscle, <0.02-0.37 ppm in kidney, <0.03-0.07 ppm in liver, and <0.03 ppm in fat were found; (2) at the 150 mg/day dose, daminozide residues were <0.02-0.06 ppm in milk, <0.03 ppm in muscle, <0.10-0.15 ppm in kidney, <0.03-0.07 ppm in liver, and <0.03 ppm in fat; and (3) at the 500 mg/day dose, daminozide residues were <0.02-0.26 ppm in milk, <0.03-0.12 ppm in muscle, <0.15-10.0 ppm in kidney, <0.12-0.37 ppm in liver, and <0.03-0.05 ppm in fat. All UDMH residue levels were at ≤0.01 ppm except for one value of 0.02 ppm at the 500 mg dose. From the results of the study, the Agency estimates that there is little transfer of secondary UDMH residue to meat and milk. For purposes of the dietary exposure analysis, the Agency used the goat data as a surrogate for beef and assumed 2.0 ppb of UDMH for residues in beef meat, kidney, fat, and milk. EPA is aware that these values may be over-estimates and that average secondary residues may be much less in regions of the country where cattle are not fed pomace from apples, grapes, and tomatoes, or peanut by-products.

In the poultry study (Uniroyal, 1987c), 40 white leghorn hens were administered by gavage doses of 0 mg, 1.8 mg, 5.4 mg, and 18 mg per bird per day for 28 days. The corresponding feeding concentrations were estimated to be 0 ppm (or 0 times the anticipated dietary intake), 20 ppm (39 x), 60 ppm (118 x), and 200 ppm (392 x). Significant transfer of secondary daminozide residue was only found at the 18 mg feeding level: <0.01-0.56 ppm in eggs, 0.09 ppm in breast, 0.08-0.09 ppm in thigh, 0.05-0.09 in kidney, <0.03-0.04 ppm in liver, and 0.11-0.26 in fat. Finite residues of daminozide were also found in eggs at the 5.4 mg feeding level (<0.01-0.09 ppm). Less than 0.02 ppm daminozide residue was found in eggs at 1.8 mg and less than 0.04 ppm was found in meat and eggs at the 1.8 and 5.4 mg feeding levels. All UDMH residues were at ≤0.01 ppm. From the results of the study, the Agency estimates that there is very little transfer of secondary UDMH residue to poultry meat and eggs. For purposes of the dietary exposure estimate, the Agency assumed levels in both poultry meat and eggs consumed by humans to be 0.5 ppb of UDMH.

Table 8 presents the residue estimates used in the dietary exposure analysis derived from the livestock feeding studies.

Table 8.

EXTRAPOLATED DAMINOZIDE AND UDMH RESIDUES DERIVED FROM LIVESTOCK FEEDING STUDIES

Commodity	Daminozide (in ppm)	UDMH (in ppb)
Beef		
meat (except kidney)	0.01	2.0
kidney	0.2	2.0
fat	0.01	2.0
milk	0.01	2.0
Poultry		
meat	0.001	0.5
eggs	0.002	0.5

b. Residue Estimate Summary

Human dietary exposure estimates are calculated using the Tolerance Assessment System (TAS) and based on residue estimates and consumption information. Because there is not a direct correlation between the food forms contained in the TAS food consumption data base and some of the forms sampled in the market basket survey, the Agency substituted some residue values as follows:

(1) peanuts - Although the Agency obtained residue data for daminozide and UDMH in peanuts and peanut butter from the market basket survey, TAS has food consumption estimates for raw peanuts, cooked peanuts, or peanut oil, but not for peanut butter. Consequently, daminozide residues of 0.8 ppm and UDMH residues of 24.9 ppb were used for calculating dietary exposure estimates from consumption of all peanut products.

(2) grapes - The Agency obtained raw grape residue information from crop field trials for daminozide (5.2 ppm) and UDMH (34.08 ppb). These values were not incorporated into the dietary exposure analysis because raw grapes or raisins treated with daminozide are not available for sale. Only Concord grapes which are processed for juice are treated with daminozide. Therefore, the Agency assumed market basket survey residues of 0.02 ppm and 1.5 ppb UDMH in grape juice.

Tables 9 and 10 list the UDMH and daminozide residue estimates, respectively, in raw and processed foods used by the Agency to calculate dietary exposure.

Table 9.

ESTIMATES OF UDMH LEVELS IN RAW AND PRODUCED FOODS

COMMODITY	PERCENT OF CROP TREATED	AVERAGE, ppb UDMH *
Apples		2.6
Apple sauce (-baby)		33.3
" " (-adult)		14.0
Apple juice (-baby)		44.0
" " (-adult)		23.9
Dried raw apples		20.8 #
Dried cooked apples		352.0 #
Cherries, sweet and sour	30	18.6
Cherry filling (and juice)		108.1
Grapes		0.0
Grape juice		1.5
Grape preserves		1.5
Nectarines	3	25.0
Peaches	3	21.3
Peaches, canned		21.3
Peanuts		24.9
Peanut butter		24.9
Peanut oil		24.9
Pears	3	11.9
Pears, canned		11.9
Beef meat		2.0
" kidney		2.0
" fat		2.0
" milk		2.0
Poultry meat		0.5
" eggs		0.5
Tomatoes, whole	10	1.6
Tomato juice	10	2.4 #
Tomato puree	10	5.3 #
Tomato paste	10	8.6 #
Catsup	10	4.0 #

* For beef, beef byproducts, milk, poultry and eggs, the residue values were extrapolated from feeding studies.

# Residue levels for dried apples includes a concentration factor of 8. For processed tomato products, the average residue of 1.6 ppb was multiplied by the following concentration factors to derive the value used in estimating exposure: 1.5 for tomato juice, 3.3 for tomato puree, 5.4 for tomato paste, and 2.5 for catsup.

Table 10. **ESTIMATES OF DAMINOZIDE LEVELS IN RAW AND PRODUCED FOODS**

COMMODITY	PERCENT OF CROP TREATED	AVERAGE, ppm DAMINOZIDE *
Apples		1.00
Apple sauce (-baby)		0.50
" " (-adult)		0.40
Apple juice (-baby)		0.50
" " (-adult)		0.40
Dried raw apples		8.00 #
Dried cooked apples		4.00 #
Cherries, sweet and sour	30	23.7
Cherry filling (and juice)		1.5
Grapes		0.0
Grape juice		0.02
Grape preserves		0.02
Nectarines	3	14.5
Peaches	3	11.3
Peaches, canned		11.3
Peanuts		0.80
Peanut butter		0.80
Peanut oil		0.80
Pears	3	8.8
Pears, canned		8.8
Beef meat		0.01
" kidney		0.2
" fat		0.01
" milk		0.01
Poultry meat		0.001
" eggs		0.002
Tomatoes, whole	10	0.20
Tomato juice	10	0.30 #
Tomato puree	10	0.66 #
Tomato paste	10	1.10 #
Catsup	10	0.50 #

* For commodity items beef, beef byproducts, milk, poultry and eggs, the residue values were extrapolated from feeding studies.

# Residue levels for dried apples includes a concentration factor of 8. For processed tomato products, the average residue of 0.2 ppm was multiplied by the following concentration factors to derive the value used in calculating exposure: 1.5 for tomato juice, 3.3 for tomato puree, 5.4 for tomato paste, and 2.5 for catsup.

c) Consumption

The Agency uses pesticide residue estimates, discussed in the previous section, and food consumption estimates to calculate dietary exposure estimates. The Agency determined exposure profiles for four different age groups: the U.S. population as a whole, nursing infants, non-nursing infants, and children aged one to six years old.

The food consumption data files used to calculate dietary exposure were derived from a nationwide survey of individual food consumption patterns of 30,770 people, conducted by the U.S. Department of Agriculture (USDA) in 1977-1978 (White, et al., 1983). The foods surveyed by USDA, such as pizza, apple pie, or beef stew, were reduced to TAS "food forms" such as wheat flour, tomatoes, mushrooms, etc. A certain amount of aggregating resulted in food consumption estimates for 691 TAS food forms. These estimates, expressed as grams of food form consumed per kg bodyweight per day, are adjusted for differences in sample size and were calculated for the overall U.S. population and 22 regional, ethnic, age, and gender subgroups. These mean estimates are assumed to reflect long-term eating habits; thus, observations of zero consumption for a particular food form were included in the calculation of that food form's consumption estimate.

Average daily consumption values were multiplied by residue information for each commodity. Residue information from crop field trials was adjusted by 1985 estimates of percent crop treated estimates. Residue data from the market basket survey were not adjusted for percent of crop treated. Multiplication of average daily consumption values and residue information results in the daily anticipated residue contribution (ARC) for each food-form and for the pesticide as a whole. The ARC represents the Agency's dietary exposure estimate.

Tables 11 and 12 describe the average daily consumption and the ARC for each commodity containing residues of UDMH and daminozide, respectively.

The dietary exposure estimates given in the following tables were determined by using TAS and the following assumptions:

(1) The average residue levels obtained in the market basket survey for the commodities sampled are assumed to be representative of the residues found in those commodities throughout the entire country.

(2) The Agency estimated residue concentrations in animal tissues by assuming the UDMH dose response curve was linear below the method's limit of detection.

(3) Apple sauce and cherry pie filling are not part of the TAS food consumption data base; however, cooked apples and cooked cherries are included. In order to calculate dietary share, the Agency used daminozide and UDMH residue data from baby applesauce to represent residues in all cooked forms of apples, including cooked apple juice, in the TAS analyses. Likewise, daminozide and UDMH residue data from cherry pie filling was used to represent residues in all cooked forms of cherries, including cooked cherry juice.

(4) As noted above, since TAS has no food consumption estimates for peanut butter, the Agency used daminozide residues of 0.8 ppm and UDMH residues of 24.9 ppb (values for peanuts from the market basket survey) for calculating dietary exposure estimates from consumption of all peanut products.

(5) Since daminozide use is restricted to grapes for juicing, exposure estimates derived from consumption of grapes or raisins were not calculated. Market basket survey residues of 0.02 ppm for daminozide and 1.5 ppb for UDMH were applied to consumption of grape juice and wine and sherry.

(6) As explained in Section II.C.3., a range of dietary exposures for tomatoes was used because available usage data has shown that no tomatoes are commercially treated and only tomato transplants intended for the home garden market are treated. Some home gardeners who grow and eat home-grown tomatoes may be exposed to 100 percent treated tomatoes and may have increased consumption patterns of tomatoes and tomato products. Average dietary risk over the entire population was also calculated based on 10 percent of crop treated. These are two alternative methods of estimating total dietary risk from tomatoes and comprise the range.

Table 11. **ESTIMATES OF UDMH DIETARY EXPOSURE FOR THE U.S. POPULATION ***

COMMODITY	AVERAGE DAILY CONSUMPTION (g food/kg bwt/day)	RESIDUE LEVELS (in ppb or ug/kg)	EXPOSURE (ug UDMH/kg/day)
Apples, fresh	0.3074	2.6	0.000799
Apples, cooked: fresh and juice	0.2004	44.0	0.008818
Dried raw apples	0.0001	20.8	0.000002 #
Dried cooked apples	0.0001	352.0	0.000035 #
Apple juice, raw	0.1709	33.3	0.005691
Cherries, raw fresh and raw juice	0.0105	5.6	0.000059
Cherries, cooked: fresh and juice	0.0251	108.1	0.002713
Eggs	0.5803	0.5	0.000290
Grapes	0.0438	0.0	0.000000
Grape juice	0.0901	1.5	0.000135
Wine and sherry	0.0842	1.5	0.000126
Nectarines	0.0130	0.8	0.000010
Peaches	0.2154	0.6	0.000129
Peanuts, raw, cooked and oil	0.0748	24.9	0.001863
Pears	0.1225	0.4	0.000049
Meat	2.2318	2.0	0.004464
Milk	1.3705	2.0	0.021068
Tomatoes, whole	0.4920	1.6	0.000787
Tomato juice	0.0551	2.4	0.000132 #
Tomato puree	0.1702	5.3	0.000902 #
Tomato paste	0.0395	8.6	0.000340 #
Catsup	0.0420	4.0	0.000168 #
TOTAL			0.000047 or 4.7 x 10^{-5} + mg/kg/day

* For commodity items meat, milk, and eggs, the residue values were extrapolated from feeding studies data. All beef, beef byproducts and poultry were combined under "meat" in this table.

Residue levels for dried apples includes a concentration factor of 8. For processed tomato products, average residue of 1.6 was multiplied by the following concentration factors: 1.5 for tomato juice, 3.3 for tomato puree, 5.4 for tomato paste, and 2.5 for catsup.

+ 1 percent of daminozide exposure (0.95 x 10^{-4} mg/kg/day) added to total UDMH dietary exposure in Table 16 used to estimate 1 percent conversion of daminozide in the gut.

Table 12. **ESTIMATES OF DAMINOZIDE DIETARY EXPOSURE FOR THE U.S. POPULATION ***

COMMODITY	AVERAGE DAILY CONSUMPTION (g food/kg bwt/day)	RESIDUE LEVELS (in ppm or mg/kg)	EXPOSURE (mg dam./kg/day)
Apples, fresh	0.3074	1.00	0.000307
Apples, cooked: fresh and juice	0.2004	0.50	0.001000
Dried raw apples	0.0001	8.00	0.000001 #
Dried cooked apples	0.0001	4.00	0.0000004 #
Apple juice, raw	0.1709	0.50	0.000085
Cherries, raw fresh and raw juice	0.0105	7.11	0.000075
Cherries, cooked: fresh and juice	0.0251	1.50	0.000038
Eggs	0.5803	0.002	0.000001
Grapes	0.0438	0.02	0.000001
Grape juice	0.0901	0.02	0.000002
Wine and sherry	0.0842	0.02	0.000002
Nectarines	0.0130	0.45	0.000006
Peaches	0.2154	0.34	0.000073
Peanuts, raw, cooked, and oil	0.0748	0.80	0.000060
Pears	0.1225	0.26	0.000032
Meat	2.2318	0.20	0.000446
Milk	1.3705	0.01	0.000014
Tomatoes, whole	0.4920	0.20	0.000098
Tomato juice	0.0551	0.30	0.000017 #
Tomato puree	0.1702	0.66	0.000112 #
Tomato paste	0.0395	1.10	0.000043 #
Catsup	0.0420	0.50	0.000021 #
TOTAL			0.000951 or 9.5×10^{-4} mg/kg/day +

* For commodity items meat, milk, and eggs, the residue values were extrapolated from feeding studies data.

Residue levels for dried apples includes a concentration factor of 8. For processed tomato products, average residue of 0.2 ppm was multiplied by the following concentration factors: 1.5 for tomato juice, 3.3 for tomato puree, 5.4 for tomato paste, and 2.5 for catsup.

+ 1 percent of exposure (0.95×10^{-5} mg/kg/day) used to estimate UDMH contribution from metabolic conversion of daminozide to UDMH when estimating risk in Table 16.

The following Tables 13 and 14 present the average daily total dietary exposure to daminozide and UDMH, respectively, for various age groups to demonstrate the differences in dietary exposure.

Table 13.

TAS ESTIMATES OF AVERAGE DAILY EXPOSURE TO UDMH FOR SELECTED AGE SUBSETS

Subset (Age and Other)	Exposure (mg/kg/day)
AVERAGE (U.S. POPULATION)	0.000047
Nursing infants (<1 year old)	0.000229
Non-nursing infants (<1 year old)	0.000410
Children (1 - 6 years old)	0.000138
Children (7 - 12 years old)	0.000071
Males (13 - 19 years old)	0.000042
Females (13 - 19 years, not pregnant or nursing)	0.000034
Females (13 + years, pregnant)	0.000027
Females (13 + years, nursing)	0.000037
Females (20 + years, not pregnant or nursing)	0.000023
Males (20 + years old)	0.000025

Table 14.

TAS ESTIMATES OF AVERAGE DAILY EXPOSURE TO DAMINOZIDE FOR SELECTED AGE SUBSETS

Subset (Age and Other)	Exposure (mg/kg/day)
AVERAGE (U.S. POPULATION)	0.000951
Nursing infants (<1 year old)	0.003396
Non-nursing infants (<1 year old)	0.005427
Children (1 - 6 years old)	0.002786
Children (7 - 12 years old)	0.001514
Males (13 - 19 years old)	0.000730
Females (13 - 19 years, not pregnant or nursing)	0.000662
Females (13 + years, pregnant)	0.000692
Females (13 + years, nursing)	0.000824
Females (20 + years, not pregnant or nursing)	0.000575
Males (20 + years old)	0.000523

2. Non-dietary Exposure

The non-dietary exposure component of non-dietary risk was calculated for daminozide and UDMH from the use of daminozide in greenhouses. This estimation was used to calculate carcinogenic risk for workers because the Agency believes that greenhouse workers are likely to receive the highest exposures of any workers.

In 1987, the Agency reviewed a greenhouse worker exposure study submitted by Uniroyal (Uniroyal, 1987e) in response to the February 6, 1986 DCI Notice. However, insufficient field spikes and controls, poor laboratory techniques, and poor tracking led to the Agency's conclusion that the data were inadequate for use in a non-dietary exposure assessment.

While no suitable daminozide exposure data were available for an exposure assessment, acceptable surrogate data were available. EPA used a recently reviewed study on exposure of greenhouse workers to acephate (Sumagic PGR) to assess non-dietary exposure.

The surrogate study (Merricks, 1987) was based on the exposure to nine workers as they filled the spray tank with pesticide, diluted the spray, and then sprayed the plants by hand in a 20' by 100' greenhouse to run-off. Dermal exposure was monitored using dosimeters (10 by 10 cm^2 foil backed alpha cellulose patches placed on exposed skin and under clothes) placed on the shoulders, chest, back, head, forearms, upper arms, thighs, and shins. Hand exposure was monitored using white cotton gloves. Separate sets of dosimeters were used during mixing/loading and applying. Dermal exposure to the nine mixer/loader replicates for all dosimeters except the hands was less than the 0.01 ug/cm^2 detection limit. The total surface area for the face, limbs (except the hands), and torso was assumed to be 18,330 cm^2. Assuming the residue on the patches (except residues on the hands) was half of the detection limit, the dermal exposure per pound active ingredient for mixer/loaders was calculated to be 87 mg/lb a.i. and 74 mg/lb a.i. for applicators. The geometric mean (unit exposure) of these data sets was calculated to be 58 mg/lb a.i. and 59 mg/lb a.i., respectively.

The Agency believes this study is suitable for surrogate use even though the majority of residue levels were below the detection limit. The failure to detect residues was not unexpected since the amount of acephate used in the greenhouse operation is minimal. For all non-detectable samples, one-half the limit of detection of the analytical method used was assumed.

Daminozide exposure and risk to mixers, loaders and applicators was calculated for typical application scenarios. The Agency used several assumptions in its exposure calculations:

(1) mixer/loaders and applicators wear long pants and long-sleeved shirts, chemical resistant gloves (providing 90 percent protection to the hands) and a protective mask;

(2) dermal absorption of UDMH is assumed to be 100 percent;

(3) UDMH contamination of daminozide is 0.005 percent; and

(4) the average greenhouse size to be treated is equivalent to about one acre (A).

In addition, the Agency assumed that the maximum label rates are used: 2 applications of 5.1 lb a.i./A on greenhouse chrysanthemums and 2 applications of 0.61 lb a.i./A on greenhouse tomatoes.

To estimate mixer/loader and applicator exposure for UDMH, the following calculation was used:

Ave. Daily UDMH Exposure (mg/kg/day) =
Application Rate x 1A treated/application x 2 applications/year x Unit Exposure x 1.00 UDMH absorbed x 0.00005 UDMH in daminozide x 1/70 kg x 365 days/year

where the Application Rate is 5.1 lb a.i./ A for chrysanthemums and 0.61 lb a.i./A for tomato transplants, and the Unit Exposure is 58 mg/lb a.i. for mixer/loaders and 59 mg/lb a.i. for applicators. Dermal exposure estimates for mixer/loaders and applicators calculated using this equation is summarized in Table 15 below.

Table 15.

AVERAGE DAILY DERMAL EXPOSURE TO UDMH

WORKER	TOMATOES (mg/kg/day)	CHRYSANTHEMUMS (mg/kg/day)
MIXER/LOADER:	1×10^{-7}	1×10^{-6}
APPLICATOR:	1×10^{-7}	$1 \text{ X } 10^{-6}$
MIXER/LOADER-APPLICATOR:	2×10^{-7}	2×10^{-6}

C. Risk Characterization

1. Dietary risks

Although the previous section presented exposure values to both the parent compound, daminozide, and the metabolite, UDMH, cancer risk was calculated using the interim UDMH cancer potency factor. As noted previously, the Agency has not received the final results of the Uniroyal UDMH carcinogenicity studies in mice and rats. Although the same types of tumors were observed in the daminozide mouse study (hemangiomas/hemangiosarcomas), only biological trends were observed. Therefore, no cancer potency factor was calculated from either daminozide study. The Agency has identified UDMH as the primary chemical of oncogenic concern at this time. The Agency has classified daminozide and its metabolite, UDMH, as category B_2 chemicals (probable human carcinogens).

The average individual lifetime risk based on an upper bound cancer potency was obtained by taking the interim UDMH Q^*_1 (cancer potency factor) from the Dose-Response Assessment [0.88 $(mg/kg/day)^{-1}$] and multiplying it by the estimates from the Exposure Assessment (given in Tables 11 and 12). The Agency did not calculate UDMH exposure from metabolic conversion of daminozide to UDMH in the gut for individual commodities. The Agency did estimate overall additional dietary risk from metabolic UDMH which is shown in Table 16. Based on an analysis of urine data from a miniature swine metabolism study conducted by Uniroyal, it appears that approximately 1 percent of daminozide is converted to UDMH in the gut. The feces, which contains a significant portion of the converted UDMH, has not yet been analyzed. (Therefore, the 1 percent UDMH contribution from daminozide conversion may lead to an underestimate of cancer risk.) Additional data are necessary for the resolution of this issue, and to evaluate the impact of any conversion to dimethyl nitrosoamine. Any conversion from daminozide to UDMH in apple, peanut and cherry products due to processing is assumed to be included in the residue estimates from the market basket survey.

Although oncogenic risks for the general population from exposure to UDMH are based on a lifetime probability at the end of 70 years, the Agency has calculated risk estimates for individual age subgroups. These risk estimates are appropriate for describing the incremental cancer risks posed by exposure to UDMH residues while individuals belong to that subgroup. As noted above in section II.B.1.b.2), dietary exposure estimates for infants and children are different from those of adults because consumption patterns vary from infancy to adulthood and because infants consume more food (particularly certain fruit) per unit body weight than adults. For these reasons, infants and children have a greater relative exposure than do adults and, therefore, may incur a substantial portion of lifetime risk during these exposure periods. Estimates of potential carcinogenic risk posed by exposure to UDMH residues for the general population, which include exposure to the various subgroups, is shown in Table 16 below. The exposure values, except for tomatoes, are found in Table 11. For Table 16, two exposure estimates have been used to derive a range of risks. In one, the exposure estimates for tomatoes used to calculate risk is ten times the value reported in Table 11. The Agency made this exposure adjustment to reflect exposure situations where the consumer grows and cans his own tomatoes, puree and/or juice. The exposure value in Table 11 reflects a ten percent of crop treated assumption. That value was derived from usage estimates indicating that 50 percent of the tomato transplants intended for the home grower market are treated and no tomato transplants used for commercially grown tomatoes are treated. The home garden market accounts for approximately 20 percent of the tomatoes consumed nationally (50 percent x 20 percent = ten percent of crop treated). This approach to calculating risk spreads total dietary risk over the entire population and does not account for those situations where people grow their own tomatoes and can tomato products. For this reason, a range of tomato risks was calculated. Risk can be calculated by assuming average national dietary exposure with 10 percent crop treated or exposure to a subset of the population with 100 percent crop treated. These are two alternative methods of estimating total dietary risk from tomatoes.

Table 16.

ESTIMATES OF UDMH DIETARY RISK FOR THE U.S. POPULATION

(interim Q^*_1 = 0.88 mg/kg/day)

Commodity	Dietary Exposure (ug/kg/day)	Dietary Risk *
Milk	0.021068	1.8×10^{-5}
Apples	0.015331	1.4×10^{-5}
Red meat	0.004464	3.9×10^{-6}
Cherries	0.002772	2.4×10^{-6}
Peanuts	0.001863	1.6×10^{-6}
Eggs	0.000290	2.5×10^{-7}
Grapes	0.000261	2.3×10^{-7}
Poultry	0.000252	2.2×10^{-7}
Tomatoes	0.000234-0.00234	$2.1 \times 10^{-7} - 2.1 \times 10^{-6}$
Peaches	0.000129	1.1×10^{-7}
Pears	0.000049	4.3×10^{-8}
Nectarines	0.000010	8.8×10^{-9}
TOTALS	**0.046715**	**4.1×10^{-5}**
	+[0.009500 estimated metabolic UDMH from daminozide]	0.84×10^{-5}
		4.9×10^{-5}

* Refer to II.C.3.b. "Uncertainties that Could Overestimate the Risk (2-3)".

Table 17 describes the average incremental risk for individuals who belong to any of the three subgroups for which dietary exposure was estimated. Annual risk was calculated by multiplying the average residue contribution for each subgroup by the interim cancer potency factor ($Q^{*}1 = 0.88$ (mg/kg/day)$^{-1}$) and then dividing the calculated risk by 70 lifetime years.

Table 17.

ESTIMATES OF RISKS
TO SELECTED AGE SUBSETS AND THE GENERAL POPULATION
FROM ONE YEAR EXPOSURE TO UDMH

Subset (Age and Other)	Dietary Exposure (mg/kg/day)	Annual Risk
Nursing infants (<1 year old)	0.000229	2.9×10^{-6}
Non-nursing infants (<1 year old)	0.000410	5.2×10^{-6}
Children (1 - 6 years old)	0.000138	1.7×10^{-6}
AVERAGE LIFETIME RISK TO THE GENERAL POPULATION FROM ONE YEAR EXPOSURE	**0.000047**	**5.9×10^{-7}**

2. Nondietary risks

The exposure estimates discussed in section II.B.2. are used as a basis for estimating non-dietary carcinogenic risk. The Agency assumed that the cancer potency factor for the dermal route of exposure is equivalent to that for the dietary route (0.88) and that the length of lifetime exposure is 35 years worked/70 years lived. To calculate non-dietary carcinogenic risk from exposure to UDMH, the Agency used the following equation:

UDMH risk = UDMH exposure x 35/70 x Q^{*}_{1}(0.88 (mg/kg/day)$^{-1}$)

Based on this calculation, the carcinogenic risks from worker exposure to UDMH is tabulated in Table 18.

Table 18.

QUANTITATIVE ASSESSMENT OF RISKS FROM EXPOSURE TO UDMH TO WORKERS APPLYING DAMINOZIDE

(interim Q^*_1 = 0.88 mg/kg/day)

WORKER	GREENHOUSE TOMATOES RISK	GREENHOUSE CHRYSANTHEMUMS RISK
MIXER/LOADER:	6×10^{-8}	5×10^{-7}
APPLICATOR:	6×10^{-8}	5×10^{-7}
MIXER/LOADER-APPLICATOR:	1×10^{-7}	1×10^{-6}

3. Uncertainties in the Risk Assessment

The cancer risks estimated by the Agency present the 95 percent upper bound risks of an individual developing cancer over a lifetime of exposure to UDMH residues. That is, there is a 95 percent certainty that the risks would be no greater than those estimated and may in fact be as low as zero. Thus, the upper bound risk estimates represent conservative estimates of risk. As with virtually all risk assessments, there are certain inherent uncertainties related to the development of the estimates. In this instance, there are additional uncertainties because the Agency's risk assessment is based on the recently available UDMH interim sacrifice data. Some of these uncertainties and their impacts on the risk estimates are described below.

a. Uncertainties that Could Underestimate Risk

(1) The UDMH study used to evaluate the cancer risks is incomplete; therefore, the response over a lifetime is not yet known. Once the study is complete, the cancer potency may go up or it may go down. However, the first tumors in the earlier cancer studies by Toth did not appear at 12 months, and the tumors were first seen in the UDMH studies by Uniroyal at 12 months. The correction factor applied to the interim results to estimate the potency at the end of the study could underestimate the overall potency.

(2) The lung tumors were not included in the potency estimates because of the high background rate of this tumor type in the tested animals. However, if final data show these tumors to be

statistically and biologically significant, they may be included in final risk calculations which could increase the potency factor.

(3) The conversion rate of daminozide to UDMH is still unclear due to lack of data. It is possible that internal conversion from daminozide to UDMH could be much greater than 1 percent which would augment cancer risks.

(4) Some additional dietary risk will occur after the Final Cancellation Notice is issued (Spring 1990) from consuming commodities legally treated prior to cancellation.

(5) No risk estimate was included for dietary exposure to NDMA. If the Agency determines from review of further data that daminozide or UDMH internally converts to NDMA, additional carcinogenic risk would have to be incorporated into the risk estimation based on NDMA's cancer potency and exposure.

b. Uncertainties that Could Overestimate Risk

(1) Mice in the study used to calculate the interim Q^*_1 for the UDMH (Uniroyal, 1988e) are dying early. Although the Agency believes that the death of these animals is due to the tumors, Uniroyal argues that the maximum tolerated dose has been exceeded. The implications of such a finding will be evaluated in the PD 4, after the Agency has reviewed the report of the study's final sacrifice which is scheduled to be submitted in January, 1990.

(2) The dietary exposure to UDMH residues in meat, milk, and eggs was extrapolated from an animal feeding study using goats and chickens which were dosed with daminozide at levels equivalent to 20 - 200 ppm. The extrapolation was based on a hypothetical animal diet of daminozide-treated apple pomace and peanut meal. The results indicate that UDMH residues in meat, milk, and eggs are at or below the limit of detection. Since a diet of apple pomace and peanut meal is likely only in areas where apples and peanuts are grown or processed, the dietary risk due to UDMH residues in meat and milk is likely to be much less than that assumed and may approach nil in many cases.

(3) The market basket survey data were taken in 1986. Use has declined since that time; therefore, exposure estimates contained in this document may represent overestimates of current levels of dietary exposure. In addition, percent of crop treated values are potentially highly variable and may lead to either an overestimation or underestimation of risk. However, future increases in daminozide use (and, therefore, dietary exposure) cannot be ruled out if the regulatory process is protracted due to administrative hearings.

III. BENEFITS ANALYSIS

A. Introduction

Daminozide is a plant regulator whose biological effects vary considerably from commodity to commodity and by variety within a commodity. Separate analyses were conducted by EPA for each of the sites for which daminozide is presently registered (Dumas, 1988; Esworthy, 1985; Gaede, 1985; Hogue, 1988; Hopkins, 1988; Kibler, 1988; Lee, 1985; Petrie, 1982, 1985, 1988; and Schneider, 1985, 1988; Szuhay, 1988). Data for the analyses were obtained from USDA; the International Apple Institute, McLean, Virginia; and from State and university sources. The peanut benefits analysis was prepared in conjunction with the Department of Agricultural Economics, University of Georgia (Allison and Bryan; 1988). The grape and cherry analyses were prepared in conjunction with Development, Planning and Research Associates, Manhattan, Kansas (Lloyd and Unger; 1988).

In addition to a complete literature search conducted by the USDA National Agricultural Library in Beltsville, MD, additional data sources include: PD 1 responses received between Fall 1983 and Spring 1984 (approximately 1500 responses), testimony from two public hearings held on daminozide use in New York State (June 1988) and, the Uniroyal Chemical Company response to an EPA request for benefits data.

Biological effects, pertinent integrated pest management (IPM) benefits, percent of crop treated, alternative chemical practices and first year economic impacts of daminozide cancellation follow for each federally labeled crop (Table III-1). Some discussion of long-term economic impacts is also included.

Much of the information presented below has not changed since 1985, when EPA previously summarized its benefits analysis of daminozide (EPA, 1985). Unless otherwise stated, the biological characteristics of the treated crops and the effects of daminozide on those crops have not changed. The major difference between 1985 and the present is that the EPA estimate of acreage treated with daminozide has declined significantly, for most of the crops (Table III-2). For those sites for which daminozide usage is believed to have decreased, benefits based on both 1985 and current usage estimates are presented. If substantial regulatory actions are not imposed against daminozide, it is possible that usage over the next few years would rise toward 1985 levels.

Use (Site/Site Category)	--- EXTENT OF USAGE --- A.I./year 1000 lbs. (% of total)	Percent of Site Treated	Key Effects	Availability of Economic Alternatives	Type	Extent		Significance
					Grower Annual Income Impacts			Insignificant in aggregate; users impacts more than offset by non-users windfall gains. Eastern McIntosh/Stayman growers will be most adversely impacted; (.30% reduction in total revenue/treated acre); come growers may be forced out of business or must replant with other varieties. Delicious total revenue implacts/treated acre are less severe (5-10% reduction).
					Users	Non-users	Total	
					($ million)			
Apples								
Red Delicious		14	improve storage, fruit color	none	-4.28	+7.73	+3.45	
Golden Delicious		13	improve storage	none	- .55	+1.93	+1.38	
McIntosh		18	stop drop, fruit color	none	-5.68	+ .98	-4.70	
Stayman		17	prevent splitting	none	-1.82	+ .29	-1.53	
All Apples		10			-14.56	+16.11	+1.55	
					Market:			
					Fresh -	Reduced quantity of 160.6 million lb. (-3.4%); price increases from $.156 to $.161/lb.		Moderate; impacts expected to diminish over time.
					Processed -	Increased quantity of 47.7 million lb. (+1.3%); price decreases from $.051 to $.050/lb.		
					Consumer:			
					Fresh -	Price increases from $.6274 to $.6401/lb. (+4.9%). Total expenditures decrease $109.5 million (-3.7%) for 160.6 million fewer pounds.		Moderate
					Processed -	Price decreases from $.3254 to $.318/lb. (-2.3%). Total expenditures increase $8.4 million (+.7%) for 47.7 million more pounds.		Insignificant;
					Total -	Total apple expenditures decrease $101.1 million/year (-2.4%) for 270.9 million fewer pounds.		

	--- EXTENT OF USAGE ---						
Use (Site/Site Category)	A.I./year 1000 lbs. (% of total)	Percent of Site Treated	Key Effects	Availability of Economic Alternatives	Type	Extent	Significance
Apples cont.					Microeconomic:-	Increased importations of fresh apples in the summer from Southern Hemisphere countries may augment seasonal supply shortfall.	minor
					Welfare/Efficiency:-	Net social cost estimates current usage (10%) of apples treated; $81 million 1985 usage (24%) of apples treated: $198 million.	minor

Use (Site/Site Category)	--- EXTENT OF USAGE --- A.I./year 1000 lbs. (% of total)	Percent of Site Treated	Key Effects	Availability of Economic Alternatives	Type	Extent	Significance	
Grapes	1985: 45.1 to 51.3 1988: Negligible	1985: 42-47% 1988: Neglig.	Increase fruit set and yield of Concord variety.	Limited	Users:	1985: 1988:	$2.4 million annual income loss. Negligible	Minor Negligible
					Consumers:	1985: 1988:	1 to 5% price increase for 2 to 5% reduction in quantitity. Negligible	Minor Negligible
Cherries	1985: Tart: 48 to 112.8 Sweet: 0.2 to 1.2 1988: Tart: Negligible Sweet: Negligible	1985: Tart: 57-72% Sweet:<2% 1988: Tart: Neglig. Sweet: Neglig.	Enhanced fruit color; uniform ripening & increased yield. Less bruising, easier pit removal.	Limited	Users:	1985: 1988:	Tart: $2.2 million net income loss/year. Sweet: Negligible. Sweet and tart: Negligible	Minor Negligible Negligible
					Consumers:		Sweet and tart: Negligible for 1985 and 1988.	Negligible
Ornamentals	1985 and 1988: 30 to 40	1985 and 1988: 90% for mums to 50% of bedding plants.	Produces compact plants with greener foliage.	Limited	Users:	1985	Costs increase $0.7 to $4.7 million for 1985 and 1988.	Minor
					Consumers:	1985:	Lower quality plants, higher prices for 1985 and 1988.	Minor
Tomato Transplants	1985 and 1988: 1.4	1985 and 1988: 50% of sales for home gardeners.	Shorter plants, more easily shipped.	Mechanical clipping	Users:		Losses of crop quality with lower grade prices and income for 1985 and 1988.	Minor
					Consumers:		Lower quality plants, higher prices for 1985 and 1988.	Minor

Use (Site/Site Category)	--- EXTENT OF USAGE --- A.I./year 1000 lbs. (% of total)	Percent of Site Treated	Key Effects	Availability of Economic Alternatives	Type	Extent	Significance	
Peaches & Nectarines	1985 and 1988: 6.5 to 18	1985 and 1988: <5%	Increased fruit color and hastened maturity.	None	Users:		$1.5-$5.5 million loss of income for 1985 and 1988.	Minor
					Consumers:		Negligible for 1985 and 1988.	Negligible
Pears	1985 and 1988: Negligible	1985: and 1988: 1-3%	Reduces premature ripening of Bartlett pears.	Foliar fertilizer	Users:	1985:	<$500,000 income loss.	Minor
						1988:	Negligible	Negligible
					Consumers:		Negligible for 1985 and 1988.	Negligible
Peanuts	1985: 175 to 225 1988: 42.5	1985: 11-12% 1988: 3%	Shorter, more erect vines; assists harvesting.	None	Users:	1985:	About $2.0 million; <1% of total grower income.	Minor
						1988:	$260,000 income loss.	Negligible
					Consumers:		Negligible for 1985 and 1988	Negligible

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[a] Usage for several minor use sites (ornamentals, tomato transplants and peaches/nectarines) appeared stable between 1985 and 1988. For apples, the economic impact estimates were based on a currently representative usage level for daminozide.

[b] Usage for mid-season/summer treatments only; usage by variety for early bearing and pruning reduction is unknown.

Table III-2. Annual Daminozide Usage by Site: 1985 and Current Market

	1,000 Lbs. A.I./Year		Percent of Site Treated	
Site	1985	Current Market	1985	Current Market
Apples	327.4-423.6	136-177	24	10
Grapes	45.1- 51.3	Negligible	42-47	Negligible
Cherries				
Tart	48.0-112.8	Negligible	57-72	Negligible
Sweet	.2-1.2	Negligible	<2	Negligible
Ornamentals	30-40	30-40	50 bedding plants 90 mums	50 bedding plants 90 mums
Tomato Transplants	1.4	1.4	50 home/garden	50 home/garden
Peaches/ Nectarines	6.5-18	6.5-18	<5	<5
Pears	Negligible	None	1-3	None
Peanuts	175-225	42.5	11-12	<3
Total	633.6-873.3	216.4-278.9		

B. Benefits Assessment - Food Uses

1. Apples

a. Usage

The crop with the largest portion of total usage is apples. In 1985, it was estimated that approximately 24 percent of all apples were treated with daminozide (Lee, 1985). Since the beginning of the 1986 season, usage of daminozide on apples has significantly declined. It is difficult to ascertain current usage since public perceptions and grower uncertainty concerning buyer acceptance may have changed substantially since the 1986 season and may affect the availability of information provided. Some major retailers of fresh apples and some major processors have refused to accept daminozide treated apples from the 1986 and subsequent seasons.

EPA's current estimate of average usage during the 1986 through 1988 seasons is about five to ten percent of all apple acreage. However, information provided by the sole registrant and other available sources together with a reasonable range of assumptions indicates that usage during these three years may have been on about five to 15 percent of the crop. It is not known what future usage would be if EPA approved daminozide for continued registration. Since any estimate of benefits must be based on some level of usage, it is assumed for the purposes of this analysis that 10 percent of the apple crop is treated annually. The 10 percent of crop treated level of usage will be referred to as "current" usage. Actual usage during the past three years and in the future may be lower or higher, with the 1985 level of 24 percent of crop treated serving as a probable upper-bound. Overall usage on fresh apples, by variety, is summarized in Table III-3. The 10 percent of crop treated estimate is higher than the 4 to 8 percent estimate cited in the January 31, 1989, Apple Tolerance Extension Document (54 FR 6392) and other Agency announcements regarding the tolerance extension and EPA's intent to proceed with proposed regulatory action cancelling daminozide. The higher percent of crop treated figure is based on additional and more in depth use information gathered in February and March 1989.

The major varieties treated with daminozide are McIntosh, Red and Golden Delicious, and Stayman. No other growth regulator is currently being used on apples.

Table III-3
Use Levels and Effects of Daminozide Cancellation - By Apple Variety

	Percent Fresh Crop Treated Current Usage[1]	1985 Usage[2]	Increased Dropped/Cracked as Percent of Treated Fresh[3]	Reduction in Storage Life[3] (Months)
Red Delicious	16	39	5	3.3
Gold Delicious	18	43	1	3.3
McIntosh	23	55	35	2
Jonathan	8	19	3	1
Stayman	24	56	35	2

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[1] Current assumed total usage distributed among varieties in same proportions as 1985 usage.

[2] From expert opinion gathered from 1984/85 telephone survey (EPA, 1985).

[3] From expert opinion gathered from 1984/85 telephone survey (EPA, 1985); supported by scientific literature and SAP hearing testimony.

i. Registered Label Treatments

In 1986, the maximum registered label rates on the Alar-85 label (EPA Registration # 400-79) were reduced from eight pounds a.i. per acre to four pounds a.i. per acre for the spring vegetative growth control treatment and were reduced from four pounds to three pounds a.i. per acre for the "mid season" and "summer" treatments. It is not known whether actual use was altered by these label changes.

(1) Spring Treatment

Daminozide is registered for one treatment per year on bearing apples if applied to bearing trees in the "spring," 10 to 14 days after bloom. The primary effects achieved are: (a) reduced vegetative growth, and (b) promotion of flower bud development resulting in a yield increase the next year. This treatment requires a much higher label rate than the "mid season" or "summer" treatment and is only used in years when the expected yield is greatly reduced because of early frost that destroyed some or all of the fruit buds. When fewer fruit buds are available for growth into apples, the tree tends to produce more vegetative growth than it would if normal levels of fruit production were occurring. Daminozide is the only plant growth regulator registered for control of excessive vegetative growth in apple trees.

Daminozide is applied to a limited extent in the spring to young non-bearing trees to bring these trees into bearing a year earlier than untreated trees. Certain varieties of young apple trees are difficult to bring into bearing. Young trees in good soil grow rapidly during early years. Usually, the trees are large enough to bear fruit before normal fruiting begins. An application of daminozide on young trees after they have filled their allotted space in the orchard will typically bring these trees into bearing the following year by reducing vegetative growth and promoting fruit bud formation. Ethephon may also be used to bring young trees into bearing but, unfortunately, ethephon can only be used on a few varieties. (Ethephon is used to enhance the red coloring on apples and is therefore limited to varieties which are red.) As a result, daminozide is the preferred treatment on non-bearing trees.

(2) Mid-Season or Summer Treatments

Most daminozide is applied to bearing trees during "mid-season" (21 days after petal fall to 70 days before harvest) or in "summer" (60 to 70 days before harvest). This treatment is primarily for decrease in fruit cracking/splitting, delay in watercore development, increases in fruit firmness and storage life, for prevention of preharvest fruit drop, and for fruit color enhancement. (The Department of Agriculture, or USDA, establishes apple color standards by which apples may be compared and graded to facilitate trade.) The two most important effects are the increase in storage life and the reduction in preharvest drop. Which of these effects is more important depends on the apple variety. In general, the later the treatment, the less effect there will be on fruit size reduction, vegetative growth reduction, and increased bloom the following year.

ii. Daminozide Treated Apples: Fresh Fruit vs. Processing

Fresh market apples are sold for immediate consumption at harvest time or are stored for sale throughout the following year. Some apples are grown specifically for processing, while other processing apples are diverted from the fresh market.

Because daminozide treatment is costly, growers are careful to treat only those apples that will benefit substantially. The multiple effects of increased storage life, reduced watercore, improved color, maintained apple firmness, reduced bruises, reduced storage scald and reduced preharvest drop result in higher quality apples which can typically be stored for longer periods of time than untreated apples. However, these effects are of much less value on apples intended for the processing market. Apples intended for processing are not kept for extended periods and therefore do not require the additional storage life provided by daminozide. Some of the other benefits of daminozide use are also irrelevant for processing apples. Therefore, apples destined for processing are treated with daminozide to a much lesser extent than apples intended for the fresh market. Since 1986, many apple processors claim to have stipulated in their contracts with growers that no daminozide treated apples would be accepted. These processors also claim to check for daminozide residues in apples by chemical analysis when they are delivered. Processors have reported success with this program.

Approximately 10 to 15 percent of the daminozide treated apples intended for fresh markets are graded down and used for processing. These apples are more likely to have daminozide applied than apples grown specifically for processing. This percentage can vary depending on weather conditions during the growing season and on the supply-demand situation in a given year.

iii. Daminozide's Effect on Specific Varieties

(1) McIntosh

Approximately 42 percent of all McIntosh apples were treated with daminozide in 1985 as compared to a current estimate of 18 percent (Petrie, 1985, 1988). The McIntosh is a cool climate, early maturing variety that is grown primarily in New York, Michigan, Idaho, Massachusetts, West Virginia, and New Hampshire. The biggest difficulty with McIntosh apples is that they tend to drop from the tree before prime picking maturity is reached. Another problem during the early part of the McIntosh harvest is a lack of adequate fruit color. Typically, the grower has an insufficient supply of adequately colored fruit to keep his pickers busy during the early part of the season followed by a large volume of fruit to harvest later when fruit condition is rapidly declining.

The Agency estimates that as much as 35 percent of the treated McIntosh crop could be diverted from the fresh market due to pre-harvest drop if treatment ceased. Dropped apples often split or crack and bruise on contact. Bruised, cracked, or punctured apples rot rapidly, and therefore, must be picked up and utilized by the processor within a few days. The registered alternative naphthaleneacetic acid (NAA) provides preharvest drop control if applied twice at weekly intervals prior to harvest. However, NAA advances maturity resulting in decreased storage life.

(2) Red Delicious

Red Delicious is by far the most popular apple variety grown. While preharvest drop is not a major problem with Red Delicious, growers do strive to harvest the fruit at the peak of quality. If picked prematurely they are not suitable for the fresh market. If picked when overly mature, they are of poor storage quality. A common practice of growers is to leave Red Delicious on the trees for an extended period in an attempt to achieve color development (extremely important for fruit grading) (Petrie, 1982). This results in over-ripe fruit that does not store well. Daminozide use is important to fruit grade by allowing the apple to hang on the tree longer in order to develop the increased red color without excessive ripening. Other undesirable effects reduced by the use of daminozide are development of watercore (internal core rotting that develops before harvest and intensifies during storage) and apple scald (diffuse browning of the apple skins during storage) (Petrie, 1982).

Approximately 34 percent of Red Delicious were treated with daminozide in 1985 as compared to a current estimate of 14 percent. Daminozide is almost always applied as a "summer" treatment to delay maturity (and thereby increase storage life). This delay in maturity also increases fruit firmness which, in turn, reduces bruises. Daminozide treated fruit can, therefore, be stored in controlled atmosphere storage from harvest to harvest while non-treated fruit can only be held until roughly July 1 of the following year.

No alternative exists which can provide both delayed fruit maturation and delayed watercore development.

(3) Golden Delicious

The major motivations for using daminozide on Golden Delicious are the same as those for Red Delicious. In short, with daminozide, a firmer, higher quality apple is achieved. The treatment also leads to more consistent yields each year, an effect more important for individual growers than for the industry as a whole. No gain in color is claimed for non-red varieties.

In 1985 daminozide was used on approximately 31 percent of the Golden Delicious crop as compared to a current estimate of 13 percent.

(4) Stayman

When used on Stayman apples, daminozide reduces fruit cracking/splitting and watercore. This effect is most pronounced in warmer mid-Atlantic climates where maturation proceeds rapidly. Approximately 41 percent of the Stayman crop was treated with daminozide prior to 1986 as compared to 17 percent in 1988.

(5) Other Varieties

Other apple varieties are not as dependent upon daminozide as are those discussed above. The Agency has limited biological information which indicates that daminozide is used to some extent on Rome Beauty and Jonathan and on early ripening apple varieties such as July Red, Raritan, Mollie's Delicious, Jerseymac and Paula Red. A daminozide application is recommended at 8 to 10 weeks before harvest on early ripening varieties to delay maturity, increase red color, reduce pre-harvest fruit drop, reduce watercore development, increase fruit firmness by 1/2 to 3 lb. pressure[1], slightly reduce fruit size, and help increase return bloom the following year (Petrie, 1982).

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[1] Fruit firmness is measured by pressing a standard probe against the surface of the fruit. Firmer apples that resist higher pressures are preferred by consumers and also can be stored for longer periods. They also have a longer supermarket shelf life.

(6) All Varieties

In recent (1988) hearings in New York State on daminozide, benefits research reports were cited which indicated reduced aphid, leafminer and red mite populations on apple trees following the use of daminozide in "mid-summer." The reduction in insect populations is related to reduced vegetative growth on daminozide treated trees, and fewer dropped apples that serve as shelter for over-wintering insects under the tree.

IPM specialist Dr. Ronald Prokopy (University of Massachusetts) reported that with the use of daminozide, more leafminers and mites can be tolerated than in non-treated blocks.

The loss of daminozide would be expected to trigger an increased need for and greater use of insecticides in order to control the higher populations of insects. This IPM program[2] will be affected if more apples drop prematurely allowing more pests to overwinter in dropped apples. Dr. Prokopy estimated that there was a 30 percent increase in fruit drop in Massachusetts in the absence of daminozide in 1986 and 1987.[3] Researchers and growers testified in New York State that it was difficult to relate increased insecticide use to the absence of daminozide, and that sophisticated IPM studies were needed to quantify effects.

b. Alternatives

Table III-4 contains a brief summary of apple benefit label claims, a column of registered alternatives, and a second column of potential alternatives in the experimental stage.

Naphthaleneacetic acid (NAA) is registered for use on apples to control pre-harvest fruit drop. Growers in New York State recently testified (1988) that they experienced a 30 percent increase in McIntosh, Cortland, Ida-Red and Spartan apple drop in the absence of daminozide even when they applied NAA. Similar effects were noted in Massachusetts and Virginia, as well. NAA is only effective for 7 to 10 days and accelerates fruit softness. Daminozide delays the onset of fruit softening

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[2] The IPM program employs behavioral, ecological and biological approaches to pest management as substitutes for pesticide use.

[3] Reduction of future pesticide use from reduced numbers of over wintering insects would provide an incentive to pick up dropped apples even if the price paid for these apples did not fully cover the cost of picking them off the ground.

TABLE III-4. Daminozide Benefits on Apples, Registered Alternatives, Potential/Experimental Alternatives

Benefit Category (Registered Daminozide Label Claim)	Currently Registered Alternatives	Potential Experimental Alternatives
1. Increased color on red varieties	No alternative [1]	X
2. Maintained fruit firmness at harvest and after a period in storage	No alternatives	uniconazole
3. Delayed fruit maturity; thereby extending the harvest period	No alternatives	X
4. Prevention of preharvest fruit drop	NAA (naphthalene acetic acid)	2,4-DB
5. Delayed development of watercore [2]	No alternatives	X
6. Scald reduced [3]	No alternatives	X
7. Reduced bruising due to increase in fruit firmness	No alternatives	X
8. Reduced vegetative growth (Spring treatment only)	Ethephon	uniconazole
9. Promotes flower bud initiation	Ethephon	uniconazole
10. Fruit cracking reduced	No alternatives	GA^{4+7} [5]

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[1] For a more detailed explanation of these benefits and possible alternatives, see Petrie, 1982).

[2] "Watercore" is an internal disorder caused by high temperature and erratic moisture conditions. Watercore often results in internal core rotting which forces early marketing due to reduced storage life.

[3] "Scald" is a disorder of apples in storage caused by the action of volatile substances given off by respiring apples.

[4] 4-6 preharvest treatments necessary.

resulting in increased storage life. In addition, daminozide enhances red color on red varieties before harvest and during the storage period.

Researchers from Canada to North Carolina have evaluated the efficacy of 2,4-DB over the past 10 years on eastern U.S. apple varieties. 2,4-DB is reportedly more effective than NAA for a longer period of time and does not stimulate fruit softening. EPA denied two emergency exemptions for the use of 2,4-DB on apples in 1986 (VA, WV) due to a lack of pre-harvest residue data.

There are currently no alternatives to daminozide for control of Stayman cracking. Researchers in VA and WV have noted promising results from 4 to 6 pre-harvest GA^{4+7} treatments (gibberellic acid). Pre-harvest residue data are needed for this use of GA^{4+7} to obtain EPA registration.

There are no alternatives to daminozide for the fruit firmness and extended storage life effects. Experimental work with the triazole compounds, paclobutrazol and uniconazole, has shown promise that these compounds may be possible replacements for daminozide for these effects and for the other daminozide claims of reduced bruising, reduced vegetative growth and increased flower bud formation.

The Agency is not aware of any experimental compounds currently under development for the daminozide label claims of increased red color on red varieties and delayed development of watercore.

c. Economic Impacts

i. Aggregate Apple Industry Economic Impacts

The most important economic effects of daminozide are related to: (1) increased storage life and (2) net increases in the quantity of apples suitable for the fresh market in any given year.[4] Beneficial effects from spring treatment which are less important but significant are: (3) a reduction in pruning costs and (4) early bearing of young trees. All label claims fit into one of these four categories.

Very little published information exists on the extent to which daminozide increases fresh apple supplies or extends storage life. To augment the literature, information and

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[4] The use of daminozide may cause apples to meet fresh grading standards that, if untreated, would have been processed.

Table III-5. First Year Economic Impacts to Apple Growers for a Daminozide Cancellation[a].

Daminozide Treatments	Change in Production (mil. lbs.)	(%)	Change in Value of Production (million $)	(%)	Change in Costs (million $)	Change in Net Income (million $)
Midseason/Summer Treatments						
Fresh	-134	-2.8	+2.1	+0.3	-3.0[b]	+5.1
Processed	+ 48	+1.3	-1.4	-0.7	-0.4[b]	-1.0
Spring Treatments						
Early Bearing[c]	- 27	-0.6	-4.3	-0.6	-1.6[d]	-2.7
Reduced Pruning	0	0	0	0	-0.2[e]	
+0.2						
All Treatments						
Fresh	-161	-3.4	-2.2	-0.3	-4.6	+2.4
Processing	+ 48	+1.3	-1.4	-0.7	-0.4	-1.0
Total	-113	-1.3	-3.6	-0.4	-5.2[f]	+1.6[g]

[a] Based on assumption of 10 percent of bearing acres treated.

[b] Change in daminozide treatment costs only.

[c] All assumed fresh; percents figured in terms of total utilization of fresh apples.

[d] Combined effect of $0.2 million treatment costs and $1.4 million harvesting costs no longer incurred.

[e] Combined effect of $340,000 increase in pruning costs and $580,000 reduction in treatment costs.

[f] Includes a $.2 million decrease in costs (explained in footnote [e]) which could not be disaggregated between fresh and processed apples.

[g] Represents <1 percent of apple industry income.

opinions were collected in 1984/85 from pomologists and other experts to gain a better understanding of the storage life impact for specific varieties in specific regions of the country. Table III-3 presents data which were used as inputs for the economic assessment. The economic impacts and net social values of these four benefit categories were estimated.

Regarding the industry in aggregate, a decline in the utilization of fresh apples can be expected (Table III-5). Considering a current usage level of about 10 percent, fresh utilization would decline by an estimated 3.4 percent (161 million pounds) if daminozide were cancelled. Of this, about 0.6 percent (27 million pounds) would be a loss in production from not bringing young trees into bearing sooner. The remaining 2.8 percent loss (134 million pounds) from utilization of fresh apples is the combined effect of increased dropped and cracked fruit as well as the decrease in storage life. Processed apple utilization would increase by an estimated 48 million pounds or 1.3 percent and non-marketed disposal losses would increase by 86 million pounds. While apple production declines by a significant amount growers also save from no longer purchasing and applying daminozide. An application of daminozide to apple trees costs from $67 to $79 per acre. The cost of treating 24 percent of the U.S. apple acreage would be about $10 million while the cost of treating 10 percent of the apple acres would be about $4 million.

EPA estimated that gross revenues to all growers will decrease by $3.6 million, but annual net income would increase by $1.6 million due to the combined cost savings of treatment costs and harvesting of induced early bearing. It should be noted that any income effects associated with an accelerated tree replacement program have not been quantitatively evaluated. Gross income for all apple growers in the U.S. was estimated in 1985 to be approximately $200 to $300 million.

The price of fresh apples at the farm gate is predicted to increase from an average of 15.6 cents per pound to 16.1 cents while the price for processing apples is expected to decrease from 5.1 cents per pound to 5.0 cents. Current use of fresh apples will decline from 4.73 to 4.57 billion pounds while processing apples will increase from 3.80 to 3.85 billion pounds.

The revenue and income impacts listed above may appear minor when spread over all apple growers. However, these aggregate figures include windfall economic gains to non-users of daminozide. While both users and non-users share the price gain in the fresh market, only users bear the losses of crop quality decreases. For the approximate current usage level (10 percent treated), users would annually lose an estimated $14.56 million while non-users would gain $16.11 million in annual net income.

ii. Variety/Regional/Distributional Economic Impacts

Based upon current daminozide usage levels as well as the nature and magnitude of output losses, the following apple varieties are expected to experience the most adverse impacts from a cancellation action: McIntosh, Stayman, Red Delicious and Golden Delicious. After analyzing shifts in total apple utilization between fresh and processed markets and the associated price changes at the national level of aggregation, the following variety/regional/distributional impact estimates were developed.

(1) McIntosh and Stayman Varieties

Relatively large percentages (18 and 17 percent) of the McIntosh and Stayman varieties are treated with daminozide with 35 percent of the treated output subject to either drop (McIntosh) or splitting losses (Stayman) should daminozide be cancelled. About 40 percent of each variety's treated output would shift to either the processed market (McIntosh-15 percent; Stayman-13 percent) or become non-marketable (McIntosh and Stayman-26 percent each). The wide price differential between fresh and processed market prices would cause daminozide users' total annual income to decrease by $5.68 million for McIntosh and $1.82 million for Stayman growers (Table III-6). For those McIntosh and Stayman producers not using daminozide, an economic windfall gain ($0.98 and $0.29 million respectively) would be associated with the higher price of fresh apples due to supply shortages.

About 78 percent of the U.S. McIntosh and 81 percent of the U.S. Stayman crops are produced in the East[5] (International Apple Institute (IAI), 1988). The remaining production of those two varieties is grown in the Central[6] states. States and other geographic areas producing these varieties that are expected to be most adversely affected by a daminozide cancellation include:

McIntosh - Michigan, New England, New York, West Virginia, and Idaho
Stayman - North Carolina, Pennsylvania, Virginia, and West Virginia.

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[5] Includes the following states: ME, NH, VT, MA, RI, CT, NY, NJ, PA, DE, MD, VA WV, NC, SC, GA.

[6] Includes the following states: OH, IN, IL, MI, WI, MN, IA, MO, KS, KY, TN, AR.

Table III-6. Impacts of Daminozide Cancellation, by Variety, on Apple Grower Annual Net Income

Type of Growers	Variety				
	Red Delicious	Golden Delicious	McIntosh	Stayman	All Variety[1]
	($ million)	($ million)	($ million)	($ million)	($ million)
Users of Daminozide	-4.28	-.55	-5.68	-1.82	-14.56
Non-users of Daminozide	+7.73	+1.93	+ .98	+ .29	+16.11
Total	+3.45	+1.38	-4.70	-1.53	+ 1.55

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[1] Includes all varieties that use daminozide as well as pruning cost increases and harvesting cost decreases for early bearing output that cannot be specified by variety. Changes in recapitalization costs, such as an accelerated tree replacement program, were not analyzed.

The fraction of daminozide treated orchards in those areas that go out of business may be sizable given the 35 to 40 percent reduction in total annual revenue per treated acre. The longer term financial viability would vary from grower to grower and would be dependent on the following factors: the proportion of the orchard acreage producing McIntosh and Stayman apples, the proportion of the orchard acreage treated with daminozide as well as the debt/asset relationship for the enterprise.

It has been suggested in hearings on daminozide in New York State that the loss of daminozide on McIntosh apples may result in the long-term need to replace 50 percent of the trees with less drop-prone varieties. The economic impacts of an accelerated tree replacement program have not been considered in this analysis.

(2) Red and Golden Delicious Varieties

About 14 and 13 percent of the Red and Golden Delicious varieties, respectively, are treated with daminozide; the most important daminozide end use effect for these varieties is enhanced storage life (Table III-3). Approximately 13 percent of the Red Delicious and 9 percent of the Golden Delicious treated output would be expected to shift either to the processed market (Red Delicious-4 percent; Golden Delicious-3 percent) or become non-marketable (Red Delicious-9 percent; Golden Delicious 6 percent). These transfers from the fresh market would cause the daminozide users' total annual income to decrease by $4.28 million for the Red Delicious and $0.55 million for the Golden Delicious. For those Red and Golden Delicious producers that are not using daminozide, an economic windfall gain ($7.73 and $1.93 million respectively) would be associated with the higher price of fresh apples due to supply shortfalls.

About 72 percent of the Red Delicious and 60 percent of the Golden Delicious crop are produced in the West[7] (IAI, 1988). The East produces 19 percent of the Red Delicious and 29 percent of the Golden Delicious crop. The Central states account for the remaining production.

Although per-acre impacts are greater for Stayman and McIntosh than for Red or Golden Delicious, the large number of Delicious acres affected, especially in Washington, make impacts on these varieties important. In addition, there is some evidence that the per-acre impacts may be more severe in the East. Although the absolute total impact will be greater in the West, some individual growers in the East may be more severely affected.

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[7] Includes the following states: CO, NM, UT, ID, WA, OR, CA.

The fraction of daminozide treated orchards that go out of the business would likely be considerably fewer than for eastern McIntosh and Stayman producers since the expected total revenue losses are estimated to range between 6 to 9 percent. The longer term financial viability of any given Red or Golden Delicious producer would be dependent on the same factors previously identified for the McIntosh and Stayman growers.

iii. Consumer Economic Impacts

At the retail level, the price of all fresh apples is expected to increase from $0.6274 to $0.6401/lb. or by an average of 2.0 percent. The price of processed apple products is expected to fall from $0.3245 to $0.3217/lb or by somewhat more than 1.1 percent. The quantities of fresh apples available for consumption are expected to decline 161 million pounds (from 4.73 to 4.57 billion pounds) as compared to an increase of 48 million pounds for processed apples (from 3.80 to 3.85 billion pounds). The price and quantity effects combine to reduce consumer expenditures by $41.4 million (fresh decrease of $42.7 million and processing increase of $1.3 million).

iv. Welfare Economic Impacts

Price and quantity changes at the farm and consumer levels were used to calculate welfare losses, which are not the same as economic impacts. Economic impacts include income transfers achieved by changes in prices; welfare impacts are the effects on society including losses (or gains) to both growers and consumers. Once all transfer effects are accounted for at the current usage level, the estimated welfare loss from a daminozide cancellation range from $18 to $81 million, with the lower end of the range believed to be closer to the expected outcome. Actual losses vary within this range, depending on the degree of competition in the apple distribution market. These figures reflect the social value (to growers and consumers) of the loss of fresh apples, the increase in the supply of processed apple products and the other costs of increased pruning and later bearing of young trees. For the 24 percent of acreage treated in 1985, this welfare loss ranges from $44 to $198 million.

A number of longer term adjustments could be made by the industry, including a shift in production to apple varieties less dependent upon daminozide. For example, Granny Smith is currently the fastest growing apple variety in terms of percentage increase in production with relatively few being treated with daminozide. An additional adjustment would be an increase in controlled atmosphere storage capacity. There is also a potential for increased imports from the Southern Hemisphere in the future to offset the summer supply shortfalls related to the decrease in storage life. It is possible that U.S. apple exports might increase in the period soon after harvest, especially if daminozide usage in the Southern Hemisphere were also to be restricted.

Very little information is available about daminozide usage in the Southern Hemisphere. Some use of daminozide is reported in Chile to control vegetative growth on Granny Smith apples. This is a variety which is normally not treated in the United

States except for treatment of young non-bearing trees to bring them into bearing a year earlier.

Impacts to the processing sector of the apple industry are expected to be minor at the national level since the quantity processed is projected to increase only 1.3 percent and the farmgate price is expected to decrease by two percent. However, in some communities in areas where high concentrations of McIntosh or Stayman apples are grown, the increase in processing apples from drops and cracks may be sufficiently large to overwhelm processing capacity. If so, the result would be a lower local price to growers and increased elimination of picked apples.

2. Peanuts

a. Usage

Approximately 1,500,000 acres of peanuts are grown in the U.S. annually. Eleven to twelve percent of these were treated with daminozide prior to 1986 (Allison, 1985). Usage since 1986 has dropped to about 3 percent of U.S. peanut acres because processors claim that they no longer accept daminozide treated peanuts (Allison and Bryan, 1988). Peanut production occurs primarily in three regions of the U.S.: the Southeast (Georgia, Alabama, Florida), Virginia-Carolina Area (Virginia, North Carolina, South Carolina), and the Southwest (Texas, Oklahoma). The Southeast is the largest peanut-producing area, accounting for over 60 percent of U.S. peanut acreage.

Before 1986, about 25 to 29 percent of the total daminozide usage was on peanuts. Of the daminozide use on peanuts, approximately 60 percent was used in the Southeast and almost 40 percent was used in the Virginia-Carolina area. In 1988, approximately 10 percent of the acreage in the Virginia-Carolina area was treated, as compared to about 2.5 percent of the acreage in the Southeast, while very little daminozide was used in the Southwest.

Daminozide is used on peanuts to control vegetative growth, producing shorter, more erect vines. Yields can be enhanced and greater poundage may be harvested as a result of decreased vine growth and better row definition. Yield increases attributable to daminozide depend partially on weather conditions and are quite variable from year to year. Yield increases from daminozide treatment are estimated to occur in 1 out of 4 years in the Virginia-Carolina Region and in 1 out of 3 years in the Southeast. Yield increases on acres treated in 1988 were estimated to average about 115 pounds per acre or 4.6 percent. (This increase is not considered to be significant.)

This yield increase is believed to occur because of an increase in harvest efficiency rather than from a direct plant growth stimulating effect. In some years weather conditions are such that the plants from adjoining rows grow together. This makes it very difficult for harvesting machine operators to determine where to drive in the field. The use of daminozide limits this growth.

b. Alternatives

There are presently no registered chemical alternatives for daminozide use on peanuts. However, a review of research reports for the past 3 years has identified diniconazole as a potential alternative for control of peanut vine growth. Diniconazole is currently in the EUP[8] review stage. It has also been suggested that occasional plants of a more erect growth pattern could be used to mark the row to aid in harvesting.

c. Economic Impacts

The overall economic impact to the peanut industry resulting from the loss of daminozide use would be negligible. The net annual income for all U.S. peanut producers is approximately $295 million with the crop having a value at the farm level of about $1 billion. Without the use of daminozide, the producer loss at pre-1986 use levels is estimated to be about $2 million (less than 1 percent of total grower net income) in the first year following a cancellation. The Virginia-Carolina area would be the most heavily affected, suffering a loss of approximately $1.4 million. The Southeast would incur a loss of approximately $0.7 million compared to a loss of $0.2 million for the Southwest.

In comparison to 1988 use levels, the total annual loss would be about $260,000. Under the current and anticipated government support systems of peanut production quotas, any production losses would be expected to last only one production season. In subsequent years, additional acreage could be brought into production to offset yield reductions.

Because the effect of daminozide cancellation on total production is so small, the impacts on consumers would be negligible.

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[8] Experimental Use Permit that could be issued by EPA under FIFRA §5.

3. Cherries

a. Usage

Daminozide use on cherries accounted for approximately 4 to 6 percent of total daminozide usage before 1984[9]. Approximately 57 to 72 percent of the tart cherry crop and less than 2 percent of the sweet cherry crop were treated annually with daminozide prior to 1984 (Lee, 1985c). For more recent years, EPA believes that virtually no daminozide has been used on tart cherries, although a low level of use has continued on sweet cherries (Lloyd and Unger, 1988).

The major tart cherry producing area of the nation is centered around the Great Lakes, with Michigan accounting for approximately 75 percent of total U.S. production. New York and Utah account for an additional 8 to 10 percent with Wisconsin, Pennsylvania, Oregon and Colorado having lower levels of production.

Tart cherries are used primarily for processing (e.g., bakery products such as pies and turnovers; juice, etc.). Approximately 97 percent of tart cherries are processed and 3 percent are sold as fresh fruit.

Daminozide benefits tart cherry production by increasing yields, improving quality and reducing losses from cherries remaining on the tree after harvest.[10] Daminozide increases harvested yields by reducing the force necessary to remove the cherry from the tree. It also increases the number of fruit buds which improves yields in the year following its use. Jointly, these two effects can produce a 10 to 15 percent increase in yield.

Quality is also enhanced by the use of daminozide primarily from its effect of increasing cherry firmness. Being firmer, cherries can be harvested and transported with less bruising. Daminozide also improves tart cherry color which increases the grade. Processing is enhanced by the increased firmness and uniform ripeness of the cherries. Firmer cherries make pit removal easier and more uniform.

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[9] Processors apparently stopped accepting daminozide treated cherries beginning in 1985.

[10] Cherries are harvested by shaking the tree and catching the cherries that fall. For this to be successful, the cherries must not be too firmly attached to the tree.

The only significant advantage of daminozide use on sweet cherries is to advance maturity for fresh sale in the roadside market (Bukovac, 1985; Nickell, 1983; Anderson et al., 1984). Because sweet cherries do not bruise as readily as do tart cherries, the primary benefit of daminozide is to bring sweet cherries to market earlier in the season (Bukovac, 1985).

b. Alternatives

Of the nine daminozide label claims for tart cherries (improves color, hastens ripening, concentrates maturity, decreases fruit removal force, prevents fruit swell, results in a uniformly firm cherry, reduces vegetative growth, lessens wind whip, promotes fruit set and buds the following year) and the three claims for sweet cherries (improves color, hastens ripening, concentrates maturity), only one alternative, ethephon, is currently registered for two of these claims. Ethephon (Ethrel Plant Regulator, EPA Registration Number #264-267) is registered for use on tart and sweet cherries to decrease fruit removal force and to concentrate cherry maturity. Ethephon is applied 1 to 2 weeks before anticipated harvest and is applied to a different spray block each day so that harvest can progress sequentially. Although ethephon may increase yields, the ethephon label warns that "concentrate applications will promote adequate loosening, but may cause adverse effects on trees such as gummosis[11] and tip die-back" or death of the tips of branches. Ethephon is not recommended for use on trees that had severe gummosis the previous year as tree damage could result. Ethephon usage has increased from 25 percent to 50 to 60 percent in an effort to harvest more uneven maturing cherries, but its use does not replace daminozide because of adverse effects on the trees.

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[11] Gummosis is the formation of clear or amber-colored exudates that set into solid masses on the surface of trees.

c. Economic Impacts

Based on pre-1986 daminozide usage levels for tart cherries (57 to 72 percent of the acreage), an annual $2.2 million income loss is estimated for a crop having a farm market value of about $60 million. Most of this loss, $1.7 million, would occur in Michigan. For sweet cherries (less than 2 percent of the acreage treated), the income loss would be $16,000, which is quite negligible relative to the approximate $100 million farm value of the crop.

For current daminozide usage levels (virtually no use on tart cherries), grower level impacts would be negligible. Consumer level impacts for either the 1985 or the current market conditions would also be negligible other than for some potential quality losses with processed cherry products.

4. Grapes

a. Usage

Prior to 1986, approximately 2 percent of the total U.S. grape acreage (33,000 to 37,000 acres), was treated with daminozide (Lee, 1985c; Lloyd and Unger, 1988). Very little daminozide has been used on grapes since 1986 (Lloyd and Unger, 1988). Almost all treated grapes were of the Concord variety with minor use on other native American varieties such as Himrod, Fredonia, and Catawba. Approximately 8 percent of U.S. grape production is of the Concord variety. Daminozide use on Concord grapes accounted for approximately 3 to 4 percent of pre-1986 total daminozide usage.

Virtually all of U.S. grown Concord grapes are processed. Concord grapes are processed for wine and unfermented purposes such as sweet juice, jelly, preserves, and dried fruit rolls.

Concord grapes are grown primarily in Washington as well as in New York, Michigan, Pennsylvania, Ohio, and Arkansas. In recent years there has been a rapid expansion of Concord grape acreage in Washington State.

The Uniroyal Alar label (EPA registration number 400-99) describes daminozide use on grapes "such as Concord" to: 1) increase berry set and subsequent yield, and 2) reduce the rate of vine growth. Daminozide can be applied anytime from first bloom to full bloom in the spring, and is not recommended on low vigor vines (less than 2 pounds vegetative weight per vine). Daminozide is registered for use at rates of 0.85 to 1.7 lb ai/acre on medium vigor vines (2 to 3 pounds vegetative weight per vine) and at 1.7 to 2.1 lb ai/acre on high vigor vines (3 pounds or more vegetative weight per vine).

Yield increases from daminozide use on Concord grapes have been demonstrated in field research in Pennsylvania, Arkansas, Ohio and New York. Daminozide increased the number of berries per cluster by an average of five when used on Concord grapes with a resulting increase in yield of 12 to 15 percent. Response of grapes to daminozide is highly variable and also depends on vine vigor and environmental conditions. Conditions which produce good natural fruit set will generally result in little additional response to daminozide.

In Arkansas, yield variation was more closely tied to vineyard vigor. It was concluded that daminozide at 1,000 ppm might insure good fruit set in years when certain environmental factors might otherwise cause yields to be low. However, when yield increases were obtained, grape juice quality was adversely affected. In Washington, Concord grape yields are normally quite high and no yield increase would be expected from the use of daminozide.

b. Alternatives

The alternative growth regulators to daminozide for use on grapes are: ethephon, gibberellic acid and NAA (naphthalene acetic acid). These are not close substitutes but may warrant consideration because of similarities for some end use effects.

c. Economic Impacts

At 1985 usage levels the short term net effect of a cancelation on the Concord grape industry was estimated to be $2.4 million annually. Given negligible current usage, grower level economic impacts are not expected.

Consumer price increases could range from one to five percent for the reduced (two to five percent) production compared to 1985 usage levels. Current consumer level impacts are expected to be negligible because of low levels of usage.

5. Peaches and Nectarines

a. Usage

Approximately 1 to 3 percent of these crops were treated annually prior to 1986 and accounted for approximately 3 percent of the total daminozide usage (Lee, 1985c). In 1988, daminozide usage on peaches appeared to be approximately the same as in 1985 (Kibler, 1988). Between 1,500 and 4,500 acres of peaches were apparently treated with daminozide in 1988. The major benefits from daminozide use include hastened ripening, concentrated maturity, and enhanced color.

b. Alternatives

There are no alternatives for daminozide use on peaches and nectarines.

c. Economic Impacts

One of the major limitations of this analysis is the small proportion of peach and, especially, nectarine acreage currently treated with daminozide; there are very few data available. No measurable national impacts are expected from a loss of daminozide since only 2,000 to 5,000 acres of peaches, one to two percent of the U.S. crop, are treated annually (almost all in the Southeast). In 1985 EPA had identified very limited nectarine acreage treated with daminozide, less than 10 acres nationwide.

One impact would be a reduction in the number of peaches available in the fresh market during the first few days of peach harvesting and an increase in the number of peaches available later in the season.

Currently, total peach industry profits are $120 to 150 million. Profits to peach growers would decrease approximately $1.5 to $5.5 million without daminozide usage in the first year after cancellation (Lee, 1985b). In the long term a portion of some varieties of peaches may be phased out and replaced with other varieties which ripen a week or so earlier.

To date, the Agency has been unable to conduct a benefit analysis on nectarines because of the lack of reliable information. Daminozide use on nectarines is believed to be negligible. Therefore, negligible consumer impacts are expected for both peaches and nectarines.

6. Pears

a. Usage

Approximately 1 to 3 percent of the total pear crop had been treated with daminozide prior to 1986. Daminozide use on pears (predominantly Bartletts) accounted for one percent or less of total daminozide usage (Lee, 1985c). The registered daminozide label recommends one treatment per year on pears grown for either the fresh or processing market in the states of Washington and Oregon only. In Washington and Oregon approximately four to eight percent of Bartletts were treated prior to 1986, depending on the weather conditions. More recent data indicate that daminozide is no longer used on any pears (Kibler, 1988).

The most important end use effect of daminozide on pears is the control of premature ripening. Pears are treated with daminozide in those years when premature ripening is stimulated by cool[12] nights. The severity of premature ripening (and, thus, the extent of daminozide usage) varies from year-to-year and between fruit growing areas. Daminozide is also used to promote flower bud initiation, control vegetative growth, bring trees to bearing, and prevent preharvest fruit drop.

b. Alternatives

Two to three foliar fertilizer applications of 10-12-0 (nitrogen-phosphorous-potassium ratio) are currently used in the upper part of the Hood River Valley to control premature ripening. This practice is not currently found in state recommendations nor has it been properly evaluated in field trials. These fertilizer applications have been adopted by many growers as a substitute for daminozide. The effect achieved is directly related to a compensation for a phosphorous deficiency in these soils. This practice is considered by growers to be less costly per acre than the use of daminozide.

c. Economic Impacts

At the 1985 usage levels, the upper bound grower level impact was $500,000 in the first year following a cancellation as compared to no expected impacts in the current market (Gaede, 1985b). Insignificant consumer impacts were expected at both the 1985 and current usage levels.

7. Tomato Transplants

a. Usage

Daminozide is used on tomato transplants grown for the home-garden market. It is used for height control to decrease the likelihood of damage in transport, to obtain a darker green color and it is thought to protect the plant from some air pollution damage. When applied to tomato transplants, daminozide retards stem elongation, delays early fruiting, and aids in concentrating maturity of the plants.

Approximately 710 million tomato plants (14.8 million flats) are sold to home gardeners yearly. Less than one half of these plants are thought to be treated with daminozide. Since four ounces of product in one gallon of water will treat 200 square feet, a total of 1,400 pounds a.i. of daminozide would be required annually for this use (Hopkins, 1989).

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[12] Ripening is stimulated by two consecutive nights with temperatures below 45°F.

b. Alternatives

No chemical alternatives to daminozide currently exist. Non-chemical alternatives cited in the Agency's 1985 daminozide analysis were clipping and water stress. Mechanical clipping of tomato transplants facilitates the spread of bacteria and fungi, but appears to be the most frequently used non-chemical technique for controlling growth of field grown tomato transplants. A new method which uses the difference between day and night temperatures has been successfully used. This is a substitute only for the height control effect of daminozide and may require modifications to greenhouses as well as increasing heating costs. These cost effects have not been quantified.

c. Economic Impacts

Growers are concerned that they will not be able to produce the same quality of plants without daminozide. Although there are no national grading standards, the market has become accustomed to and demands plants of a specific size. If growers cannot meet these demands they will receive a lower price for what are perceived as relatively lower quality plants or they may discard a significant portion of their crop entirely. This could result in substantially reduced net profits in the short run. Since there would likely be a short supply of high quality plants, growers may be able to recoup some of their losses by demanding a higher price for those high quality plants that are produced. How much of these losses the growers can recoup depends on the overall market situation and the perceived value of the product.

Retailers may have to alter their overall standards and market a larger portion of plants that are perceived of as lower quality at a lower price. One major concern is that retailers may have to reduce prices to sell the transplants more quickly because they will not remain in saleable condition for as long as daminozide treated plants.

C. Benefits Assessment - Non-Food Uses

The following is a summary of benefits for the registered non-food use of daminozide. Usage and alternatives are presented, as well as possible impacts to the industry without daminozide usage.

1. Ornamental and Greenhouse Plants

a. Usage

Daminozide usage on ornamental and greenhouse plants accounted for approximately 4 to 5 percent of total daminozide usage prior to 1986. Daminozide is registered as a growth retardant and is used primarily on potted chrysanthemums and bedding plants, particularly petunias and marigolds. Daminozide is also registered and used on hydrangeas, marigolds, zinnias, asters, cut chrysanthemums, azaleas, poinsettias, and gardenias. Approximately 90 percent of the over 33 million potted chrysanthemum plants sold and as much as 40 to 50 percent of the total 65 million square feet of bedding plants grown in the U.S. in 1984, were treated with daminozide. These usage values remained constant through 1988 (Esworthy, 1985).

Daminozide is widely used on various ornamental and greenhouse crops because of its ease of application (the label directions indicate to spray to runoff), predictable plant response, and low chance of plant injury (phytotoxicity). Generally, daminozide causes potted and bedding plants to be more compact and have greener foliage without significantly affecting flowering. Thicker stems and deeper green leaves result in plants that have a more pleasing appearance to the purchaser.

Besides improving plant attractiveness, plant growth regulation with daminozide is important in facilitating optimum shipping and plant longevity. Daminozide also reduces leaf injury to petunias caused by the air pollutants ozone and sulfur dioxide, retards neck stretching of cut chrysanthemums, controls height of hydrangeas, promotes the development of additional buds on azaleas which helps keep the plants compact, reduces elongation of poinsettias, and helps produce compact gardenias.

b. Alternatives

The most likely registered alternative chemical growth retardants are ancymidol (A-Rest^R) or paclobutrazol (Bonzi^R). Ancymidol is registered for chrysanthemums, bedding plants and poinsettias, but is currently used primarily on container grown lilies and various cultivars of dahlias and tulips. Paclobutrazol is also registered for use on chrysanthemums, poinsettias and bedding plants.

Although ancymidol has been shown to be effective on chrysanthemums, bedding plants (only 4 species on the label are in common with daminozide) and poinsettias, grower acceptance is still low. Paclobutrazol and ancymidol are reported to be extremely active, requiring growers to test application rates more carefully to determine the desired growth retardation effect. Accurate dosage levels and spray volumes are critical and there is a relatively low margin for error. Growers are concerned with overtreating with ancymidol and paclobutrazol because of potential phytotoxicity, as well as with undertreating which would result in uneven growth. There is also some indication that ancymidol does not produce the intense greening of foliage that occurs with the use of daminozide. The chemical cost of using ancymidol is as much as 3 to 8 times higher than daminozide.

Chlormequat (Cycocel[R]) is another potential alternative registered for use on azaleas, poinsettias and ageratum. However, daminozide and chlormequat are registered as a tank mix for poinsettias, which is becoming the preferred treatment over each chemical used alone.

Non-chemical alternatives include withholding water or fertilizer, controlling light, and maintaining lower temperatures. The non-chemical alternatives are considered to be less desirable practices causing adverse effects such as delayed flowering, discoloration and small leaves.

c. Economic Impacts

Significant impacts on potted chrysanthemum and bedding plant growers would be expected if daminozide use were to be discontinued. The portion of potted chrysanthemums (90 percent) and bedding plants (40 to 50 percent) treated with daminozide have a wholesale value of $78.5 million, and $83.6 to $104.5 million, respectively. Without daminozide, growers could incur substantial dollar losses due to increased production costs (alternative chemicals are 3 to 8 times more expensive), discarded plants, and a higher proportion of the crop being of a lower quality, thus, receiving a lower price. Information on the cost of mechanical clipping was not available.

Although there are no national grading standards, the market has become accustomed to and demands plants of a specific size. If growers cannot meet these demands they will receive a lower price for what are perceived as relatively lower quality plants or they may discard a significant portion of their crop entirely. This could result in substantially reduced net profits in the short run.

Since there would likely be a short supply of high quality plants, growers may be able to recoup some of their losses by demanding a higher price for those fewer high quality plants that are produced. How much of these losses the growers can recoup depends on the overall market situation and the perceived value of the product. Retailers may lower their overall standards and market a larger portion of relatively lower quality plants at a lower price. One major concern is that retailers may have to reduce prices in order to sell the transplants more quickly since they will not remain in saleable condition for as long as daminozide treated plants.

IV. RISK/BENEFIT ANALYSIS AND DEVELOPMENT OF REGULATORY OPTIONS

A. Introduction

As explained in Chapter I, FIFRA requires the Agency to determine if the use of a pesticide meets the statutory standard for registration by balancing the risks and benefits of use of the pesticide. This Chapter summarizes in section B the toxicology and exposure data for daminozide and UDMH, and the resultant risk from dietary and non-dietary exposure to UDMH. Section C of this Chapter summarizes the Benefits of daminozide use and the potential economic impacts of cancellation. Section D presents an evaluation of considered regulatory options. Section E summarizes the Agency's preliminary regulatory decision.

B. Risk Summary

The Agency has determined that the daminozide metabolite, UDMH, is a potent carcinogen and that lifetime dietary exposure to it at current levels poses significant risks to the public. This determination is based primarily on several key factors:

(1) EPA's classification of both daminozide and UDMH as B_2 chemicals, probable human carcinogens, based in part on recent long-term studies and supported by results of earlier studies showing the same vascular and lung tumors;

(2) an estimated increased lifetime cancer risk of 4×10^{-5} to the general population (5×10^{-5} if metabolic conversion to UDMH is considered) based on a potency estimate of 0.88 $(mg/kg/day)^{-1}$ derived from a UDMH study in mice;

(3) the commodities that may contain daminozide and/or UDMH residues are staples in the diet of the general population; therefore, the population at risk is very large and the total number of potential cancer cases is substantial;

(4) the likelihood that children are a high risk group because a disproportionate share of lifetime exposure (approximately 20 percent) occurs in the first five years of life. (NOTE: The Agency has sought the advice of the National Academy of Science as to whether children may have a greater sensitivity to carcinogenic agents such as UDMH than adults because the tumors generated by exposure to UDMH in the high dose UDMH study are formed early in life.); and

(5) results indicating that NDMA, a known carcinogen, is also a metabolite of daminozide.

At this time, the Agency does not believe that non-dietary exposure to daminozide and/or UDMH poses substantial risks to workers. The information underlying these determinations is detailed in section II and summarized below.

Recent studies have shown UDMH to be a potent carcinogenic agent in mice, producing statistically significant increases in liver hemangiomas/hemangiosarcomas and lung adenomas in both sexes. Although increases in the incidence of hemangiosarcomas and combined hemangiomas/hemangiosarcomas were not statistically significant by Fisher's exact pairwise comparison for daminozide, significant dose-related trends were noted for these tumor increases by Cochran Armitage trend analysis. The Agency believes the oncogenic response seen in the daminozide studies is likely caused by the presence of UDMH in the test material and/or metabolic conversion to UDMH.

Earlier cancer studies, while limited in scope and quality, provide qualitative support for the conclusions drawn from the more recent, more scientifically sound studies. Specifically, the same uncommon tumor types have been observed in both sexes of three animal species in both the earlier and more recent studies, including the interim sacrifice data from an ongoing UDMH study.

Based on the one-year interim sacrifice data from the ongoing UDMH study in mice, an interim cancer potency factor of 0.88 $(mg/kg/day)^{-1}$ was calculated for the combined incidence of hemangiomas and hemangiosarcomas. (Because the cancer potency factor was derived from the results of a one-year interim sacrifice, rather than two-year results, it could well be an underestimate if the incidence of tumors increases with age.) The interim potency factor was used in combination with UDMH dietary exposure values to estimate risk.

The Agency believes the most reasonable estimate of dietary exposure to apples, apple products, peanuts, peanut butter, grape juice and cherry products should be based on residues from the 1985-1986 crop season since usage may return to 1985 levels if daminozide's registration were allowed to continue. The 1986 market basket survey was conducted by Uniroyal in three sampling intervals: winter, spring and fall of 1986. The residue data from the first two sampling periods reflect the 1985 crop for fresh apples and likely represent the 1985 crop for all processed products (apple juice, grape juice, cherry filling and peanut butter). Residues in apple juice, raw apples, peanuts, and cherries accounted for 48 percent of the total UDMH dietary exposure. Theoretical residues estimated from livestock feeding studies for those in meat, milk, and eggs account for 50 percent of the total UDMH dietary exposure used in calculating dietary risk.

The exposure values used in the cancer risk assessment are the average UDMH residue values from the market basket survey, the animal feeding study estimates, and crop field trial data for sweet cherries, grapes, nectarines, peaches, pears, and tomatoes. The field crop data were adjusted for the estimated percent of the 1985 crop treated. All residue values were multiplied by the food consumption factors found in Chapter II - Table 11, to obtain the exposure values used in the risk assessment for UDMH. Risks were calculated for the general population, which includes exposures during childhood, as well as an estimate of lifetime risk that occurs from exposure during infancy (the period of highest exposure per unit of body weight.) Estimates of dietary risk to the general population from UDMH exposure are found in Table II-16. Risk from exposure during infancy to UDMH is shown in Table II-17.

There are several alternatives to daminozide that provide some of the same biological effects. These alternatives, and the data available for each on oncogenicity, mutagenicity, teratology, and reproduction are presented in Table IV-1 and summarized below.

Although considerable data for two chemicals, paclobutrazol and uniconazole, have been submitted to the Agency, the data for the most part have not been completely reviewed. A fairly complete data base is available for ethephon with no major health effects of concern noted at this time. Additional data on the incidence of certain tumor types in controls is needed to complete the oncogenicity potential assessment for ethephon. The Agency issued a preliminary notification of Special Review to registrants of 2,4-DB and its analog 2,4-D in September, 1986, based on an epidemiology study that suggested a link between phenoxy herbicides, including 2,4-D, and increased incidences of cancer among farmers handling such chemicals. In March, 1988, EPA announced its proposed decision (53 FR 9590) not to initiate a Special Review of 2,4-D, 2,4-DB and 2,4-DP because the epidemiology study which was the basis for the pre-Special Review concerns was judged to be inadequate to assess the carcinogenic potential of these chemicals.

The Agency has calculated non-dietary cancer risk estimates for greenhouse workers based on exposure to UDMH when mixing and loading daminozide as well as when applying daminozide to chrysanthemums and tomato transplants. Non-dietary exposure estimates were multiplied by the interim cancer potency factor for UDMH (0.88 $(mg/kg/day)^{-1}$). Lifetime cancer risks for those individuals working with greenhouse chrysanthemums and tomato transplants were greatest for mixer/loader/applicators (1×10^{-7} and 1×10^{-6}, respectively). Carcinogenic risks were lower for individual mixer/loaders and applicators. However, it should be noted that many of these workers would also be receiving the same

Table IV-1.

SUMMARY OF THE TOXICITY OF THE ALTERNATIVES TO DAMINOZIDE

CHEMICAL	ONCOGENICITY	MUTAGENICITY	TERATOLOGY	REPRODUCTION
Diniconazole	NDA	NDA	NDA	NDA
Uniconazole	rat = * mouse = *	*	rat = * rabbit = *	rat = *
2,4-DB	rat = -ve mouse = -ve[3]	+ve#	NDA	rat = -ve[3]
Ethephon	rat = supp.[3] mouse = supp.[3]	-ve/+ve	rat = -ve rabbit = -ve	NDA
Gibberellic acid	NDA	-ve	-ve[3]	NDA
Paclobutrazol	mouse = * rat = *	-ve	rabb. = *	rat = *

NDA = no data available
-ve = negative
+ve = positive
3 = additional data required

* = data awaiting review
supp. = supplementary
# = based on limited gene mutation data

level of dietary exposure discussed above. Hence, for this subgroup, consideration of risk should reflect combined dietary and non-dietary exposures.

C. Benefits Conclusions

The Agency has reviewed the available information on benefits of use of daminozide and has concluded that, with the exception of use on ornamentals and bedding plants, the overall impacts of cancellation would be insignificant to minor on both growers and consumers. In assessing benefits, the Agency considered usage information from 1985, which reflects "normal" usage before any regulatory action was proposed, and from 1988 when use was significantly lower.

One benefits consideration, not readily quantifiable but recognized, is the nature of the benefit resulting from daminozide use. Unlike pesticides used to protect the existence of the crop, many of the biological benefits of daminozide use are related to the appearance of the crops.

There are no alternatives to daminozide that alone will accomplish all of the growth regulator benefits attributed to daminozide. For the principal apple varieties that have historically had the highest percent of crop treated with daminozide, there are no alternatives for the key biological effects of use (i.e., Red Delicious - reduce watercore, improve storage and fruit color; Golden Delicious - improve storage; McIntosh - delay premature ripening, prevent fruit drop, improve fruit color and increase storage life; Stayman - prevent splitting).

The impact of cancellation of registration for use on apples at 1988 usage levels is estimated to be insignificant to the apple industry in the aggregate; the overall effect on all growers is estimated to be an annual income increase of $1.5 million. Growers of some varieties, particularly Eastern McIntosh and Stayman, may be most adversely affected. Growers of these two varieties are estimated to have annual income losses of $5.68 and $1.82 million, respectively, and may have a greater than 30 percent reduction in total revenues per treated acre; some growers may not be able to continue to grow and sell apples or may need to replant to other apple varieties or crops over time. Non-users of daminozide may experience a gain in income from higher market apple prices.

A cancellation of daminozide is expected to reduce the supply of fresh apples by 160 million lbs (annual U.S. production is 8 billion lbs), and apples available for processing may increase by 47.7 million lbs. These changes are estimated to result in a corresponding three percent price increase and a two percent price decrease for fresh and processed apple products.

The net social cost (total society cost) of cancellation of daminozide use on apples based on 10 percent of the crop treated is estimated to range from $18 to $81 million as compared to $44 to $198 million for 1985 usage levels. (The 10 percent estimate is higher than the earlier 1989 estimates, discussed in conjunction with the apple tolerance extension Federal Register Notice, which were 4 to 8 percent. The increase in the usage estimates is from additional and more in-depth use information gathered in February and March 1989.) The Agency expects the net social cost will be closer to the lower end of the presented ranges because of the large transfer payments expected between the farm and retail markets.

For the remaining food crops (grapes, sweet and tart cherries, pears, peaches, nectarines, and peanuts), grower level economic impacts of a cancellation based on 1988 usage estimates are estimated to be negligible except for peach/nectarine growers who could suffer a minor $1.5 to $5.5 million loss of income. Based on 1985 usage estimates, annual grower level impacts may be minor for all crops except sweet cherries, which are estimated to be negligible. Annual income losses for these crops were estimated as: grapes - $2.4 million; peaches/nectarines - $1.5 to $5.5 million; pears - <$500,000; and peanuts - $2.0 million.

Economic impacts of a daminozide cancellation upon consumers for non-apple food crops at 1988 usage levels is estimated to be negligible. Based on 1985 usage levels, consumer impacts are estimated to be negligible for sweet and tart cherries, peaches/nectarines, pears, and peanuts. However, grape products may experience a one to five percent price increase and a two to four percent reduction in the marketed quantity, which is minor.

Tomato growers may incur income losses from reduced crop quality. Consumers may experience higher prices and lower quality plants based on 1985 and 1988 usage data.

If the use of daminozide on ornamentals and bedding plants were cancelled, both users and consumers could be significantly affected. Based on 1985 and 1988 usage data (90 percent of chrysanthemums and 50 percent of bedding plants treated), users might suffer cost increases from $700,000 to $4.7 million. Accordingly, consumers could expect to pay higher prices for lower quality plants.

D. Regulatory Options

The Agency has concluded that, when daminozide is used as currently registered, the combined dietary risk from all daminozide treated food crops outweighs the benefits based on either 1988 or 1985 usage levels. Therefore, the purpose of evaluating regulatory options is to determine if there are modifications in the terms and conditions of use that would result in benefits outweighing risks for some or all uses. The specific regulatory options considered and the resultant reduction in exposure and risk are discussed below.

1. Apples

a. Reduction in Application Rate and Increasing Pre-Harvest Intervals

Reducing application rates can, in general, be a practical means for reducing exposure. The use rate on apples was reduced in 1986 as an interim exposure reduction measure and further reductions would adversely affect the efficacy of daminozide. Since daminozide is a systemic growth regulator and is incorporated into the flesh of the fruit, EPA believes that increasing the pre-harvest interval would not generate a significant reduction in the level of daminozide and UDMH residues present in the fruit.

b. Reducing UDMH Exposure from Apples, Apple Sauce and Juice, and Apple Pomace used in Animal Feed

With apples accounting for the major percentage of daminozide's use, any meaningful dietary exposure reduction would have to come from lower UDMH residues in raw apples, apple products, and apple pomace used as cattle feed. Thirty three percent of UDMH exposure comes from residues found in fresh apples (2 percent) and apple products (31 percent). The Agency estimates that cancer risks based on dietary exposure to apple products alone would be sufficient to warrant consideration of regulatory action. Theoretical residues in milk (45 percent) and meat (9 percent) account for 51 percent of UDMH's estimated dietary exposure used in calculating risk. Although no actual market basket residues have been found in milk, meat, poultry or eggs, residues are possible because data from feeding studies show that daminozide and UDMH residues do transfer from apple pomace as well as from other daminozide treated foods that are fed to cattle such as grape pomace, and peanut byproducts.

Two possible modifications to apple use were evaluated. Prohibiting use on apples for processing would theoretically eliminate UDMH residues in apple sauce and juice and residues in animal and cattle feed from apple pomace by almost 90 percent (assuming other animal feeds, such as peanut by-products, were also eliminated). This restriction would lower dietary risk to almost 10^{-6}, but the Agency still believes that the risks outweigh benefits. Limiting use to certain varieties could also further reduce exposure. In particular, the Agency looked at limiting use to McIntosh and Stayman apples intended for the fresh market. Both varieties are widely marketed as fresh apples and the Agency estimates that growers of these varieties would suffer the biggest economic losses from the cancellation of daminozide. The McIntosh and Stayman varieties account for approximately 15 percent of total apple treatments. A rough estimate of the UDMH dietary contribution from McIntosh and Stayman apples is 0.3 percent of the total apple/apple product contribution (2 percent UDMH from all fresh apples x 15 percent of fresh apples that are McIntosh and Stayman). The total risk contribution from McIntosh and Stayman fresh apples is approximately 4×10^{-8} (1.35×10^{-5} risk from all fresh apples and apple products x 0.3 percent, the percentage of exposure from these two varieties).

While such a reduction in risk would appear to warrant reconsideration of the risk/benefit assessment, as a practical matter, the Agency does not believe it can reasonably ensure that use will be confined to these varieties, or to apples that are not processed. Many users grow more than one variety and virtually all growers hope to be able to sell as much of their harvest as possible in the fresh market where prices are significantly higher. Rejected apples, often treated, are then sold for processing. Daminozide products have had a caution included on the label since 1986 warning growers not to treat apples intended for processing. The high number of positive samples for apple juice as seen in recent surveys, such as those conducted by Consumers Union (Consumer Reports, May 1989), show that treated apples are being used in processed apple products. [Consumers Union reported in the May, 1989, issue that 23 out of 31 (71 percent) adult apple juice samples contained daminozide residues above the 0.02 ppm detection limit of the analytical method used and an overall average residue of 0.11 ppm. As a note, however, the high number of positive samples in the Consumers Union report may be in part a result of the sampling area, New York City, where McIntosh and Stayman apples are more likely to be incorporated into processed apple products. Carryover in trees sprayed in previous years may also account for some of the positive samples.]

Thus, although there are very restrictive use limitations that theoretically could result in significantly reduced risks, the Agency does not believe that for daminozide use on apples, a practical, enforceable way of ensuring adherence to these limited use restrictions can be achieved.

2. Peanuts and Cherries

Because apples account for such a large percentage of daminozide's use, cancellation of daminozide use on peanuts and/or cherries alone, the two food commodities with the highest exposure contribution after apples (not including theoretical residues in meat and milk), would have little effect on total dietary risk. Risk would be reduced from 4.1×10^{-5} to 3.7×10^{-5}. Benefits are estimated to be minor for peanuts ($2.0 million in net income loss to growers; <1 percent of total peanut farm income) and minor to negligible for cherries (sweet cherries, negligible; tart cherries, $2.2 million in net income loss) based on 1985 data. Based on 1988 usage, grower and consumer losses are estimated to be negligible. Even if apples were cancelled, the remaining risk from peanuts (1.6×10^{-6}) and cherries (2.4×10^{-6}) both exceed the estimated benefits and cancellation is being proposed.

3. Grapes, Pears, Peaches/Nectarines, and Tomatoes

Cancellation of daminozide on any or all of these crops would not appreciably affect total dietary risk. Individual dietary risk from exposure for these crops is presented below:

COMMODITY	**DIETARY RISK**
Tomatoes	$9.3 \times 10^{-7} - 9.3 \times 10^{-6}$
Grapes	2.3×10^{-7}
Peaches	1.1×10^{-7}
Pears	4.3×10^{-8}
Nectarines	8.8×10^{-9}

Total dietary risk from exposure to these crops is approximately 1×10^{-6} (using the low end of the tomato risk range). These risks are based on 1988 percent of crop treated and therefore reflect the lower end of the risk range. If usage returned to 1985 levels, the risks from dietary exposure would increase but it would still be likely that most individual crop risks would be below 10^{-6}.

Impacts on growers and consumers of sweet and tart cherries, peaches, pears, nectarines, peanuts and grapes would be minor or negligible based on 1985 or 1988 usage. There may even be various intangible benefits to the grower from renewed consumer confidence supported by the fact that daminozide and UDMH residues would no longer be present in the marketplace. Although the dietary risk from exposure to peanuts, grapes, pears, and peaches/nectarines is small, the Agency has concluded that these risks outweigh the negligible to minor benefits and cancellation is being proposed.

Although an estimated 50 percent of tomato transplants grown for home garden use are reportedly treated with daminozide, quantitative economic impacts could not be calculated because of a lack of specific data. Loss of daminozide on tomato transplants would result in "lower quality" plants and higher prices to the consumer with a loss of crop quality and subsequent income to the grower based on either 1985 or 1988 usage data. In balancing the risks and benefits of daminozide use on tomatoes, the Agency was particularly concerned about home gardeners whose source of fresh tomatoes and tomato products may totally be from treated plants. The 20 percent of tomatoes grown by home gardeners likely represents the highest percentage of home grown versus commercially grown crop of the major food commodities. The Agency believes a significant portion of the population, particularly in warmer geographic regions where tomatoes can be easily grown, may be experiencing risks closer to the upper end of the risk range. Further, the risk range for tomatoes was based on "average" consumption patterns. It is possible that people who can tomato products are likely to eat more tomato products than those who do not.

The Agency has therefore concluded that the risks of 9×10^{-7} to 9×10^{-6} (1985 and 1988 usage estimates are the same) outweigh the benefits and is proposing cancellation. The Agency recognizes that, in some instances where significant benefits have been demonstrated or assumed, it has considered risks of this magnitude sufficiently negligible to forego regulatory action (see, e.g., "Delaney Paradox", 53 FR 41104, October 19, 1988). However, the Agency's current assessment of the benefits related to these minor uses indicates that they are so insignificant as to be trivial. Accordingly, given some level of risk and almost no benefit, the risk/benefit balance shifts in favor of cancellation. The Agency acknowledges that more data on economic impacts are needed and is soliciting information during the public comment period.

4. Ornamentals and Bedding Plants

With regard to the use of daminozide on ornamentals and bedding plants, the Agency estimated the greatest individual lifetime cancer risks posed by non-dietary exposure to UDMH from use on greenhouse ornamentals to be 1×10^{-6}. In addition, the Agency believes that annual grower and consumer losses (as high as $4.7 million in an industry with an annual wholesale value of $78.5 to $104.5 million) would be substantial if the greenhouse uses of daminozide on ornamentals were cancelled. Therefore, the Agency believes that the benefits of continued use clearly outweigh the carcinogenic risks for non-dietary use of daminozide on ornamentals and bedding plants and is proposing to continue the registration of these uses.

E. Regulatory Decision

The Agency has concluded that all food uses of daminozide should be cancelled because the resultant risk from dietary exposure to the daminozide and/or its metabolite, UDMH, outweigh the benefits of continued use on each food commodity.

The Agency will also propose in the near future to revoke the daminozide tolerances for all raw agricultural commodities as well as the daminozide food and feed additive regulations for processed commodities.

EPA has determined that the benefits outweigh the risks for the non-food uses of daminozide and that all registrations for use on ornamentals and other uses on bedding plants should be retained without modifications to the terms and conditions of registration.

F. Existing Stocks

Pursuant to FIFRA section 6(a)(1), "the Administrator may permit the continued sale and use of existing stocks of a pesticide whose registration is cancelled [pursuant to section 6 of FIFRA] to such extent, under such conditions, and for such uses as he may specify, if he determines that such sale or use is not inconsistent with the purposes of [FIFRA] and will not have unreasonable adverse effects on the environment." For purposes of this action, EPA defines the term "existing stocks" as any quantity of daminozide products subject to this Notice that:

(1) is in the United States,

(2) was formulated, packaged, and labelled for use on the date of publication in the FEDERAL REGISTER of this Notice, and

(3) is being held for shipment or release or was shipped and released into commerce prior to the date on which the registration of the product is cancelled pursuant to this Notice.

The Agency has determined that no further shipment, distribution, sale or use of existing stocks of daminozide products labelled for cancelled uses will be permitted after the effective date of cancellation. In addition to daminozide products in channels of trade, this existing stocks prohibition is applicable to daminozide products in the hands of end users. The Agency made this determination based on several factors. First, daminozide is a systemic pesticide that remains in plants for a considerable time after application and may result in residues in subsequent harvests. In addition, much of daminozide use is on crops for processed foods that can remain in the market system for long periods of time. In both of these instances, allowing use of existing stocks would effectively extend potential exposure well beyond the final use season - an option that the Agency believes will result in unreasonable adverse effects on human health. Finally, because of the extensive regulatory history leading to the cancellation of daminozide, users will have ample time to prepare themselves for this eventuality by exploring alternative options, including discontinuance of daminozide use.

Accordingly, after publication in the FEDERAL REGISTER, no person who is a registrant or producer of a product subject to this Notice may release for shipment existing stocks of any product whose registration is cancelled or denied by this action or no persons may distribute, sell, offer for sale, hold for sale, ship, deliver for shipment, or receive and (having so received) deliver or offer to deliver existing stocks of products whose registration is cancelled by this action. EPA has found this disposition of existing stocks to be consistent with the purposes of FIFRA.

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